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## FEMALE INFERTILITY

### OUR DIAGNOSTIC RESPONSIBILITIES

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CHICAGO

It is amazing that women tend to accept full responsibility for their failure to conceive, and it is equally inconsistent that communications on this problem are usually entitled "female sterility." The term female sterility implies that husbands are usually fertile, whereas in my own experience more than half of the husbands must either share or accept full responsibility for a childless union. A man cannot be absolved from responsibility for his wife's failure to become pregnant simply because his semen contains some actively motile spermatozoa; we must be more critical than that in our evaluation of seminal fluid.

To call these women sterility problems is inappropriate for other reasons. There are few individuals, either men or women, who can be considered absolutely fertile and, conversely, very few who are absolutely sterile. Human beings, at best, are only relatively fertile. Furthermore, there must be varying degrees of relative fertility even though there is no scale by which such relative fertility can be measured; e. g., many couples of whom both the husband and the wife must be of high fertility have no difficulty in achieving pregnancies as promptly and as frequently as they wish; other couples of whom one spouse is apparently normally fertile and the other only moderately fertile have children—but it may be months before the wife becomes pregnant. On the other hand, the marriage of individuals who are both of low fertility is likely to result in no progeny. Occasionally such unions are terminated; subsequently each spouse remarries and both achieve pregnancies by the second marriage, possibly because each new spouse is an individual of high fertility.

Furthermore, the majority of childless marriages do not result from an absolute sterility either in the husband or in the wife: they are instances of relative infertility brought about by a multiplicity of factors in both spouses; some of these factors may seem trivial but, added together, they are sufficient to prevent conception. Success in the relief of barrenness therefore depends on thorough examination of both the husband and the wife followed by systematic elimination of every possible contributing cause from each of them.

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The physician whom the wife consults is obligated to make a diagnosis, i. e. to discover all factors which may contribute to her infertility. He must not jump at conclusions and he dare not take anything for granted. His examination must be thorough, and as a minimum it should include (1) a complete general physical survey, (2) a search for gross abnormalities in the female generative tract, (3) an evaluation of the male factor, (4) study of the uterine cervix, (5) testing of the oviducts for patency and (6) an investigation of the endocrine system.

At her first visit the wife is subjected to a general physical examination. At this time one should also attempt to evaluate the function of the glands of internal secretion from her height, weight and body configuration, together with the distribution of fat and hair.

The lower genital tract is searched for infection—leukorrheal discharges, especially those resulting from cervicitis, are important. Not only is the cervix inspected but its canal is tested with cervical dilators to determine whether it is adequately patent.

The size of the uterus has some significance. Hypoplasia of the uterus may be suspected either from the presence of an elongated small cervix with tiny external os or from the difficulty experienced in palpating the corpus; the length of the uterine cavity is easily ascertained with a sound. Long ago I learned that some young women with moderate hypoplasia of the uterus became pregnant with amazing alacrity.

Retrodisplacement of the uterus, with anterior tipping of the cervix away from the seminal pool, has probably been overemphasized as a cause of infertility. Following Sampson's description of endometriosis, retroflexion assumed a more important role in this problem. Pelvic endometriosis may follow retrograde menstruation through the oviducts, and such backflow of menstrual blood is most likely to occur when the cervix is stenotic, the uterus is retroflexed or fibroid tumors distort the uterine cavity. Pelvic endometriosis is found frequently in a private clientele, especially among young women who fail to become pregnant. Thus far there is no convincing explanation for the low fertility of women with pelvic endometriosis; their oviducts are patent; they ovulate, and they may become pregnant—but not frequently. This condition should be suspected when the uterus is retroflexed and fixed, the ovaries are enlarged and adherent, and when there are tiny, firm, sensitive nodulations either in the cul-de-sac, in the rectovaginal septum or on the uterosacral ligaments. If the patient complains of dysmenorrhea that has been acquired during adult life and consists, in part, of pain referred to the rectum, one can be almost certain that one is dealing with pelvic endometriosis. In my experience endometriosis is a most frequent cause of infertility.

Gynecologists disagree about the relationship of uterine fibroids to a woman's failure to conceive; I doubt that they are often responsible for infertility.

Masses in the region of the oviducts and ovaries may be either residues of pelvic inflammatory disease or cystic ovaries, signifying either previous inflammation, endometriosis, endocrine imbalance or new growths. All are of importance in the problem of relative fertility.

The next step, not the last, is an examination of the husband's semen. Preferably, the specimen should be obtained after several days of continence. The semen is collected and transported in a clean glass container, not in a rubber condom, which tends to inhibit the motility of spermatozoa. The semen should be kept at room temperature, since spermatozoa die more quickly at body temperature. 1. One should determine the amount of semen (it should be about 4 cc.); most of our specimens are obtained by coitus interruptus, frequently some of the specimen is lost and I doubt that the volume of a specimen is of great import. 2. The number of spermatozoa per cubic centimeter is vital (the normal is about 100 million per cubic centimeter); every specimen of semen must have a sperm count. 3. Eighty-five per cent of the spermatozoa should be actively motile and migrating at room temperature for hours after ejaculation. 4. One should also search for adventitious elements, such as leukocytes and red blood cells. 5. The morphology of the spermatozoa is studied in stained smears (at least 80 per cent should be normally formed).

Most husbands consider themselves fertile if they are sexually potent; they actually believe that "patent oviducts plus a potent male" should invariably result in a pregnancy. Too often physicians are guilty of further pampering this masculine ego by accepting, as normal, any specimen of semen which contains some actively motile spermatozoa. The following observation by Mazer and Israel [1] is extremely pertinent: "The degree of fertility of the male decreases, and approaches zero, with diminution in the volume of semen, decline in the number and viability of spermatozoa, and with an increase in the percentage of abnormal forms." Consequently the accepted criteria for a normal specimen of semen are reiterated: amount, 3 to 4 cc.; number of spermatozoa, approximately 100,000,000 per cubic centimeter; motility, 85 per cent actively motile and migrating at room temperature; morphology, 80 per cent normally formed; and, finally, there should be no more than an occasional leukocyte or red blood cell per high power field. Husbands must be referred to a urologist if their semen does not conform in all respects to the aforementioned criteria. Although only one spermatozoon is required to fertilize an egg, the husband with a reduced sperm count is essentially sterile.[2]

Failure to recognize deficiencies in semen has been responsible for many failures in the management of barren marriages. Possibly it would be best if all husbands were examined by a urologist, but it must be by one who is especially interested in the problem of male infertility.

Patency of the oviducts is determined by transuterine insufflation with carbon dioxide gas. I prefer an apparatus which receives carbon dioxide at a constant pressure, measures the volume of gas which passes into the abdomen and includes a mercury manometer. The ideal time to make this test is three to seven days after the conclusion of a menstrual period. Under normal conditions, gas flows through the oviducts freely at a pressure that fluctuates between 40 and 80 mm. of mercury. If gas fails to pass through at 180 to 200 mm. of mercury the pressure should not be carried higher for fear of traumatizing the oviducts. The position of the cannula in the uterus is changed several times, and gas pressure each time allowed to rise to 180 mm., before it is assumed that gas is not going to pass through the oviducts at that test. Insufflation tests should be repeated three or four times, preferably at monthly intervals, before one is justified in concluding that the oviducts are actually blocked. Intrauterine injection of a radiopaque substance is seldom indicated; this procedure is reserved for patients who wish to consider surgical relief from occluded oviducts. The chief value of hysterosalpingography is to demonstrate the exact site of tubal obstructions. Lipiodol and similar oily opaque mediums are not innocuous; sometimes they cause tubal inflammation and, if retained in the oviducts, they may initiate a foreign body reaction.

The next examination is a Huhner test. This should be performed at the time of ovulation, i. e. twelve to fourteen days before the expected onset of a menstrual period. The wife reports for examination several hours after coitus. One should still find spermatozoa in the vaginal vault, but they will probably be immotile because spermatozoa are killed rather quickly by normal acid vaginal secretions. In normal persons the clear glairy endocervical mucus, aspirated with a Luer syringe two to four hours after intercourse, should contain 3 to 15 actively motile spermatozoa per high power field.

Consequently, the Huhner test demonstrates (1) whether intercourse has been consummated normally, (2) the ability of spermatozoa to ascend into the cervical canal and (3) the effect of endocervical secretions on the spermatozoa. Dead spermatozoa in the cervical canal are indicative of endocervical hostility; this usually results from an endocervicitis where there is a mucopurulent discharge. Eradicating an endocervicitis is one of the most direct methods of improving fertility.

After one has examined the wife's genital organs for gross abnormalities, determined the status of the husband's spermatogenesis, investigated the patency of the cervix, uterus and oviducts, checked on the delivery of semen to the cervix and the reception accorded spermatozoa by endocervical mucus, the final diagnostic step is an endocrine survey. This is the least satisfactory phase of the problem, from the standpoint both of diagnosis and of treatment.

Healthy women of childbearing age, who menstruate normally and with some degree of regularity, probably also ovulate fairly regularly. On the other hand, individuals without gross genital pathologic changes, who either menstruate infrequently, flow irregularly and scantily or bleed continuously, probably do not ovulate —such menstrual disorders usually result from disturbed function by the glands of internal secretion.

There is no direct method of proving that a woman ovulates. We are compelled to rely on presumptive evidence, namely the microscopic appearance of the endometrium at the onset of a menstrual period. Endometrial biopsies for this purpose are obtained with a suction curet, preferably within a few hours after the first show of menstrual blood. It is assumed that a woman has ovulated if her endometrium shows the normal effect of corpus luteum hormone stimulation. Such progesterone effects are hypertrophy of stroma cells, corkscrew hypertrophy of uterine glands, secretory swelling of their lining epithelial cells and good develop-

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2. Huffman, J. W.: New Factors of Clinical Significance in the Study of Human Spermatozoa, Surg., Gynec. & Obst. **73**: 228, 1941.

ment of spiral arteries so that they extend into the compacta, or surface layer, of the endometrium. Although it is more difficult to interpret endometrial biopsies taken after the onset of menstrual bleeding, this is the safe time to take them. If one takes biopsies a few days before the expected onset of a menstrual period, sooner or later he will take a biopsy of a pregnant uterus.

For women who fail to ovulate, as well as for many others, additional diagnostic studies may be desirable, viz., x-ray films of the sella turcica, basal metabolic rates, blood cholesterol determinations and sugar tolerance tests.

In addition to the foregoing physical conditions, it is probable that there are psychologic factors which contribute to infertility; e. g., adoption of an infant is sometimes followed rather promptly by a pregnancy, and this despite years of previous infertility.

The diagnostic survey must be a painstaking search for every factor which might contribute to the barren marriage. The physician's next obligation is a systematic elimination of each and every contributing cause found in both the husband and his wife. We must not restrict treatment to a single major factor while neglecting the minor, more trivial causes. Due consideration to these apparently nonessential conditions may account for the success of some clinicians where others fail. However, the details of treatment do not fall within the province of this presentation.

## CONCLUSIONS

1. Either the husband or the wife may be responsible for her failure to conceive; usually both are at fault and both must be examined thoroughly.

2. The diagnostic survey of such cases should be concerned with (*a*) the wife's general physical condition, (*b*) the status of her genital organs, (*c*) spermatogenesis, (*d*) delivery of semen to the cervix, (*e*) ascent of spermatozoa into the uterus, (*f*) patency of the oviducts, (*g*) ovulation and (*h*) the ability of the endometrium to receive and nourish a fertilized egg.

3. All physicians must search more carefully for deficiencies in seminal fluid; husbands should be referred to an interested urologist if the semen is not absolutely normal.

4. Most childless marriages result from a multiplicity of factors; all must be systematically eliminated.

5. One is likely to fail in the management of infertility cases unless one receives wholehearted cooperation from the husband as well as the wife; both must submit to the entire diagnostic study and both must follow through with all indicated treatment.

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## ABSTRACT OF DISCUSSION

DR. ROBERT M. GRIER, Evanston, Ill.: Large and numerous uterine tumors may only indirectly cause sterility, not because conception is impossible, but because pregnancy does not carry to term, which results in a barren marriage. Endometriosis notoriously results in sterility or single child marriage. The explanation for this is as yet lacking, especially as the tubes are usually patent. Endocrine disturbances, as are evident from a careful physical examination and laboratory tests, leave us too often without procedures for therapy. Only hypothyroidism seems to offer much in the way of help. Administration of thyroid to these patients under close observation has been so repeatedly successful that its use cannot be overlooked. Why this is true is still not clearly explained. It is amazing to me how many women have been informed by physicians that pregnancy is impossible or unlikely because of retrodisplacement of the uterus. This condition in itself almost never is the sole cause of failure to conceive. When one thinks of the number of spermatozoa deposited at each male emission and their extreme motility when the male is healthy, it is hard to believe that they can fail to reach the cervical canal in sufficient numbers, even though the cervical opening is not bathed in the seminal pool. Probably 50 per cent of the women I see show absolutely no condition which could cause barrenness. Frequently the husband refuses to cooperate. It has been my plan to require examination of the husband's spermatozoa before submitting the woman to tubal patency or other tests. If the husband will not cooperate to this extent I refuse to go further, and frequently the matter is dropped after the first visit. This may be due to the man's ego or to a wife's fear of the harmful psychologic effect it will have on her husband. The fear of discovery of an old venereal infection plays its part. It also may be inconvenient because of the husband's working hours. I have found that the Huhner test is the easiest to accomplish. Even though this test is not completely accurate, certainly if abundant normal and active sperm are seen we cannot attach too much responsibility to the husband. But if this condition is not found I then ask the husband to consult an interested urologist. It appears to me that with the improvement in education of the public in these matters more and more cooperation is being attained. When the husband is pronounced normal by a urologist or the Huhner test shows him to be healthy, then the Rubin test is done. It is very gratifying to see the good results following this test. Patency may be established following some weak obstruction. This is suggested by a manometer reading which rises at first to 160 mm. of pressure and then descends to normal around 70 or 80. I am quite skeptical of the value of endocrine therapy other than thyroid medication. Its workings are still in the realm of conjecture and are not without danger.

DR. RALPH A. REIS, Chicago: It is strange that sterility has become a problem of the gynecologist. After all, 30 to 40 per cent of all barren marriages result from deficiencies of the male partner be they systemic, endocrine, developmental or inflammatory in character. Furthermore, an additional 20 to 40 per cent of barren marriages are indirectly male in origin in that the male is the donor and the female is the recipient of the infection which results in genital tract occlusion. The barren marriage always presents a double problem; that is, the necessity of investigating the fertility of both husband and wife. The intelligent layman has come to understand that an investigation of his fertility is not an investigation of his virility. Resentment or lack of cooperation is therefore gradually fading away even though such education is both slow and difficult. I should like to agree heartily with Dr. Gardner's procedure in evaluating the male partner. My difficulties in interesting urologists in male fertility studies has led me to carry out these studies myself. The site of the occlusion of the female generative tract may be the uterine tubes or the cervix. Salpingitis has always been considered the more common cause of such obstruction and is most frequently found by investigators of patients of clinic level. It has been my experience that the incidence of salpingitis in private patients is much lower than the generally accepted level. I found that 60 (48 per cent) of 125 consecutive private patients complaining of sterility had definite cervical disease. This was in contrast to the 21 (17 per cent) with evidence of salpingitis or pelvic inflammatory disease. Dr. Gardner has said that "eradicating an endocervicitis is one of the simplest methods of improving fertility." This was proved in our series and reported last year by Dr. Bernick and me; 35 of our patients were treated by cervical cautery alone. No other treatment was used for this group of patients and pregnancy followed in 27 of the 35 within twelve months. Like Dr. Gardner, I cannot produce ovulation, normal menstrual function or normal pituitary-ovarian relationships. But I am much more optimistic concerning the endocrine phase of the barren marriage than Dr. Gardner professes to be. By far the largest percentage of endocrine problems which I see are due to hypothyroidism, the one type of endocrine dysfunction which can be successfully treated. Hypothyroidism is so common in my experience that basal metabolic determinations are carried

out routinely on husband and wife as a primary diagnostic procedure. Much will be lost by considering the basal metabolic rate as a secondary or additional diagnostic study in the same category as sella turcica x-ray studies, cholesterol determinations and sugar tolerance tests. Basal metabolism rates should be determined primarily. Hypothyroid patients do respond to simple replacement therapy and one dollar's worth of thyroid substance will frequently accomplish infinitely more than one hundred dollars' worth of x-rays, biologic assays and endometrial biopsies. I feel that the majority of childless marriages are due to a single cause and that only a minority have multiple causes.

Dr. V. D. Lespinasse, Chicago: My work has been largely with the obstructive lesions in the male in relation to sterility. The commonest type of obstruction is in the lower portion of the epididymis. My contribution to this mechanical problem is in taking one definite epididymis tube and joining it to the vas. My results are about 65 to 70 per cent successful. The pelvic vas, when obstructed, needs a cross operation. That operation is a vas anastomosis and carries practically 100 per cent success, so that mechanical problems in male sterility, even after one has diagnosed them as being mechanical, still require a further diagnosis as to where that obstruction is and what the appropriate surgery is to relieve that obstruction.

Dr. Henry K. Sangree, Philadelphia: The male is at fault in about 50 per cent of nonfertile marriages. Teamwork is necessary in a study of infertility and should include an associated survey by the gynecologist, obstetrician, internist, endocrinologist and urologist. The latter by training and experience is particularly fitted to examine and treat the male partner in a barren marriage. About twenty years ago the average couple seeking relief for infertility had about a 20 per cent chance, even when they consulted physicians interested in this field, whereas today many groups of expert workers effect cures ranging from 40 to 50 per cent. Between two and nine factors are often present in the study of both partners. Dr. Meaker says that 4.7 is the average. In a consecutive study of 132 men, azoospermia was present in 12 of the first 100 cases and aspermia was present in 26. Chronic prostatitis was present in 30 cases. Endocervicitis is considered an obstructive to action by the sperm as it enters the uterus. I did 5 epididymovasostomies with 1 success. Gonococci were present in 28 per cent and, of course, many men with such infections have children. A positive serologic reaction was present in 8 per cent, even though the wife had a negative serologic reaction. A severe type of varicocele was present in 8 per cent of the cases. Penile hypospadias was present in 2 per cent. In these cases of penile hypospadias it is almost necessary for the man to wear a cover and cut a tiny hole in it, in the end, so that the spermatic fluid can come through. Hypothyroidism was present in 28. Mumps had been present in 13 cases and bilateral orchitis in 9 cases. I don't think that mumps has much to do with infertility in my study, but if a man has had bilateral inflammatory orchitis in conjunction with mumps after he has reached adulthood then I think it may be a cause. I think it is advisable to do a testicular biopsy before operation to see if there are sperm in the testes. A hundred million was the number that Dr. Gardner gave. Sixty million was the count in New York by Dr. Hotchkiss on 100 men who were perfectly normal and who had children.

Dr. A. R. Abarbanel, Washington, D. C.: The evidence at hand shows that there is a period of about twenty-four hours, ranging from twelve up to (rarely) seventy-two hours, in which sperm can penetrate cervical mucus. This fortunate event usually occurs around the tenth to fourteenth day of the menstrual cycle but has been found occasionally as early as the fifth or as late as the twentieth day of the cycle. During the remainder of the cycle the cervical mucus is not penetrable by sperm, except during menstruation. Therefore, in performing the Huhner test, one is merely going on chance. In the past few months I have seen 3 patients who were told that their tubes were absolutely closed because no gas went through at 220 mm. of mercury pressure. As a matter of fact there was present only tubal spasm. After these patients had taken oral methyltestosterone for a total dosage of 50 to 150 mg., repeated tubal insufflation revealed the carbon dioxide going through at 40 to 80 mm. of mercury pressure, while the pattern of tubal motility was normal. Two of these patients are now pregnant. The third point I would like to present is that of the management of threatened and habitual abortion. I have been able to confirm Karnaky's original contention that large doses of diethylstilbestrol will effectively maintain gestation in these patients. The therapeutic plan in the case of threatened abortion is as follows: 25 mg. of oral diethylstilbestrol at once, followed by 5 mg. every fifteen minutes until bleeding and/or cramps stop. Usually 50 to 100 mg. does the trick. Then 5 mg. three times daily is given until "life" is felt. After that 5 mg. daily until the thirty-second week of gestation. At the first sign of bleeding or cramps, 25 mg. is to be given followed by the routine outlined. In the case of habitual abortion, as soon as the diagnosis of pregnancy is confirmed the patient is placed on 5 mg. of oral diethylstilbestrol three times daily and continued until the thirty-second week. Pregnant patients tolerate these doses of diethylstilbestrol easily with no side effects. The rationale for the use of large doses of estrogen is this: Most abortions result from vascular discontinuity between the trophoblast and the maternal endometrial circulation. By maintaining vascular integrity and continuity, the estrogen maintains the pregnancy.

Dr. C. J. Stamm, Philadelphia: The excessive acid reaction of the vagina was simply mentioned and passed over. Tests recently have shown that the spermatozoa need sugar to live; therefore some one ingeniously got together a formula (glucose and isotonic solution of three chlorides), thus reducing the hyperacidity of the vaginal secretion. Whether it was the Ringer's solution or the sugar I can't say, but the addition of sugar to the douche is of real value. I strongly advise the use of this solution as a douche at night, particularly before coitus. We have heard about the inability of some women to conceive, yet with all of our present knowledge about rhythm no one today has mentioned the fact that it might not be a bad idea to instruct our patients that the proper time for them to try to conceive is at or about the time ovulation is due. In the question of the failure of the tubes to give a proper response to insufflation the previous speaker advocated the use of testosterone. I use an ordinary antispasmodic, any one will do, given to the patient for two or three days before the time when we are ready to do our insufflation. I have found repeatedly that the simple antispasmodic was sufficient to relax the musculature of the tubes and that the tubes previously reported closed were really patulous. Operations on the cervix are simple. Conization and cauterization will clear up cervicitis and endocervicitis. A word of warning—don't go too deep and do it at the proper time, which is immediately, or soon after the menstrual flow ceases, in order to prevent secondary hemorrhage, which usually occurs if it is done after the seventh day following menstruation.

Dr. J. P. Greenhill, Chicago: I should like to add something to this discussion only because of the remarks made by the last speaker concerning a douche preparation which is said to help women become pregnant. A number of physicians met to organize a new society interested in the study of infertility. This group consisted of specialists in obstetrics, gynecology, urology, physiologic chemistry and psychiatry. Among the subjects discussed was vaginal acidity and douches. It was unanimously agreed that the amount of acidity of the vagina has no bearing on fertility or infertility. Therefore douches aimed at overcoming hyperacidity or hypoacidity of the vagina or directed at prolonging the motility or life of spermatozoa in the vagina are of no value. In recent years, endometrial biopsies performed to determine the presence or absence of ovulation have revealed a relatively high incidence of unsuspected tuberculosis of the endometrium in sterile women. Since in almost every case of endometrial tuberculosis the oviducts are involved, tuberculous salpingitis is one of the causes of infertility which must be considered.

Dr. George H. Gardner, Chicago: I wish to thank all of those who have discussed my paper. They have added many interesting points which time limitations prevented me from discussing as a part of my presentation.

# THIOURACIL TREATMENT OF ANGINA PECTORIS

## RATIONALE AND RESULTS

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Total thyroidectomy has proved an effective therapeutic procedure in the treatment of angina pectoris (Lev and Hamburger,[1] Blumgart, Levine and Berlin,[2] Levine and Eppinger,[3] Claiborne and Hurxthal,[4] Clark, Means and Sprague,[5] Scherf,[6] Singer[7] and others).

Eppinger and Levine[8] expressed the belief that the complete removal of the thyroid gland alters the response of the cardiovascular system to epinephrine and that it is the alteration of this mechanism which may, in a measure, be responsible for the relief of anginal pain. Likewise Shambaugh and Cutler[9] reached the conclusion that the beneficial effect of removal of the thyroid gland in angina pectoris may be due, in a part at least, to a diminished effectiveness of the physiologic output of epinephrine. Barbour and Prince[10] ascribed to epinephrine a causative role in angina pectoris as early as 1915, when they showed that it constricts the coronary arteries of monkeys and probably also of man, in contrast to those of other mammals.

Today the dominant role of adrenergic discharges in the pathogenesis of angina pectoris on effort, emotion, exposure to cold and the like appears established by numerous experimental and clinical facts:

1. The specific anoxiating effect of epinephrine on the heart muscle (Barcroft and Dixon,[11] Evans and Ogawa,[12] Gremels,[13] Rein,[14] Green and his associates[15]) which decidedly exceeds the oxygen requirement for the simultaneous increase of its muscular action (Gollwitzer-Meier, Kramer and Krüger[16]).

2. The physiologic discharge of epinephrine into the blood stream under the very conditions which typically elicit anginal symptoms, namely exercise, emotion and exposure to cold (Cannon[17] and others).

3. The accumulation of epinephrine in the heart muscle during exercise and exposure to cold.[18]

4. The production of anginal pain through injection of epinephrine in persons with coronary sclerosis (Levine, Ernstene and Jacobson,[19] Katz, Hamburger and Lev,[20] Cottrell and Wood[21]) and also in normal persons[22] (Wenckebach[23]).

5. Abnormally intense discharges of epinephrine and related substances[24] into the blood stream during physical exercise in angina patients.[25]

6. The presence of abnormally high concentrations of epinephrine and related substances in the heart muscle of patients who have suffered from anginal symptoms.[26]

7. The analogy between the effects of epinephrine on the electrocardiogram and the electrocardiographic changes occurring during anginal attacks (Vesa,[27] Lepeschkin,[28] Katz, Hamburger and Lev[20] and others).

8. The occurrence of anginal symptoms in patients with adrenal medullary tumors (Bauer,[29] Nuzum and Dalton,[30] Brunschwig, Humphreys and Roome[31] and others) and their disappearance after removal of the tumor (Lenhartz[32]).

9. The provocation of anginal symptoms by agents which are known to stimulate the secretion of epinephrine, such as insulin (Brandt and Katz,[33] La Barre and Houssa,[34] Kugelmann,[35] Raab,[36] Schönbrunner[37]) and tobacco smoking (Cannon, Aub and Binger,[38]

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Stewart and Rogoff,[39] Kobro,[40] Raab,[36] Külbs,[41] Deneke,[42] Strauss [43]).

10. The prolonged absence of anginal symptoms paralleling the disappearance of the abnormal discharges of epinephrine in angina patients following roentgen irradiation of the adrenal region [23] (Hutton,[44] Hadorn,[45] Schittenhelm,[46] Lippross,[47] Raab and Soule [48]).

It is well known that the thyroid hormone sensitizes the heart to the effects of epinephrine (Steppuhn, Naumova and Ugarova,[49] Wise and Hoff,[50] Aumann and Youmans,[51] Sawyer and Brown,[52] Sadae,[53] Lütolf [54]). In recent experiments a striking increase in the cardiac mortality of rats resulting from the injection of epinephrine was brought about by pretreatment with thyroxin, and a number of thyroxin

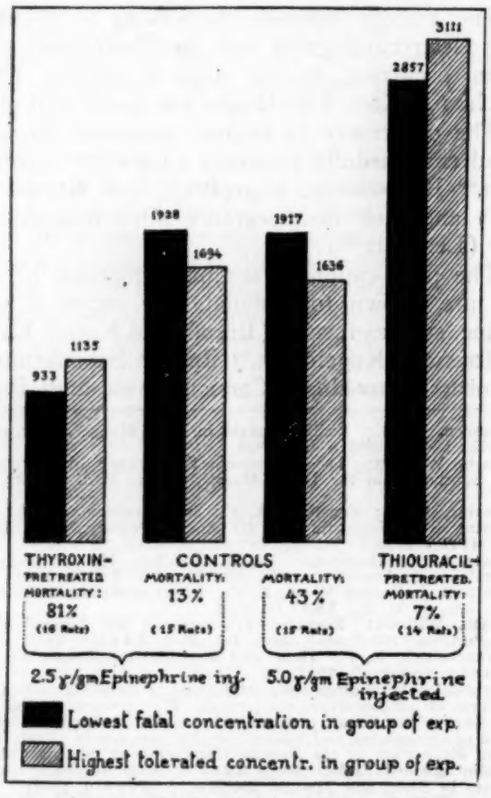


Fig. 1.—Accumulation of injected epinephrine in the heart muscle of the rat. The columns and figures represent the total colorimetric readings in the heart muscle (method explained in articles referred to in footnote 18 and in second reference in footnote 24). They include the basic concentration of epinephrine, sympathin and related substances plus the amounts of epinephrine accumulated following injection, partly in a chemically modified form. These experiments demonstrate the sensitization of the heart to epinephrine through thyroxin and the opposite, heart-protecting effect of thiouracil.

pretreated animals succumbed to myocardial accumulations of epinephrine which were considerably below the minimum level which had been found to be fatal in normal rats [55] (fig. 1). Furthermore, angina pectoris is a not uncommon complication of hyperthyroidism (Lev and Hamburger,[56] Brill [57]).

The observations of Riseman, Gilligan and Blumgart,[58] concerning an unchanged effect of intravenously injected epinephrine on blood pressure, pulse rate and systemic oxygen consumption in angina patients before and after thyroidectomy (except in cases of fully developed hypothyroidism) are not dealing with the criteria of angina pectoris (i. e. paroxysmal myocardial anoxia). Consequently they cannot be held against a fundamental role of epinephrine in the mechanism of angina pectoris. The theory that I [58a] have advanced maintains that the anginal symptoms on effort, emotion, exposure to cold and the like are caused essentially by the locally anoxiating effect of acute excess accumulations of epinephrine and sympathin in the heart muscle whose coronary arteries are sclerotic and which is sensitized to epinephrine through the thyroid hormone.

Thiouracil, as an agent which selectively suppresses the formation of thyroxin in the thyroid gland (Astwood [59]), appeared theoretically as a possible substitute for total thyroidectomy, whose shortcomings (risks of surgical intervention, irreparable loss of thyroid function) prevented its general acceptance.

It could be shown in recent experiments on rats that the sensitivity of the heart to epinephrine is much reduced after pretreatment with thiouracil and that considerably larger myocardial accumulations of epinephrine are tolerated by thiouracil treated rats compared with untreated animals [55] (fig. 1).

Also the epinephrine sensitivity of the heart of 10 physically healthy persons was found diminished after three months of thiouracil administration regarding pulse rate and anoxic changes of the electrocardiogram, while the blood pressure reactions were not significantly altered.[60]

Beginning in October 1943 thiouracil [61] was given to 10 patients with typical angina on effort. The patients were urged to keep a record of the daily number of their attacks on calendar sheets. When these records were kept in a negligent fashion the approxi-

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mate number of attacks was estimated from the patient's description.

Periods of thiouracil treatment of 6 patients were followed by or alternated with periods of placebo administration without the patients' knowledge.

Leukocyte counts were taken at weekly intervals during the early stages of the treatment and later on at increasingly longer intervals.

## REPORT OF CASES

CASE 1 (fig. 2).—E. P., a woman aged 63, a housewife, had no serious illnesses previous to the onset of anginal symptoms seven years before. These increased gradually in intensity and number until a maximum was reached, which had persisted during the past three years without interruption. Two to five attacks of several minutes' duration occurred every day, consisting of a painful oppression underneath the sternum and in the basal metabolic rate to —3 per cent and an almost complete disappearance of the anginal symptoms persisting for another month after the thiouracil tablets had been replaced by placebos. Subsequently, while placebos were given over a total period of eleven months, the anginal symptoms reappeared slowly. However, the attacks remained much less frequent than before treatment, even when the basal metabolic rate had returned toward its original level and the electrocardiogram showed renewed signs of myocardial anoxia (fig. 5).

CASE 2 (fig. 3).—J. G., a man aged 70, an inmate of the "city farm," who had syphilis at the age of 46, "radically" treated, suffered during the past four years from attacks of pain underneath the sternum radiating into the left shoulder and arm, of two to three minutes' duration, sometimes longer; they occurred on walking, emotions, exposure to cold, after meals and now and then at rest; he had one or more attacks almost every day. Eight months before he had one very severe

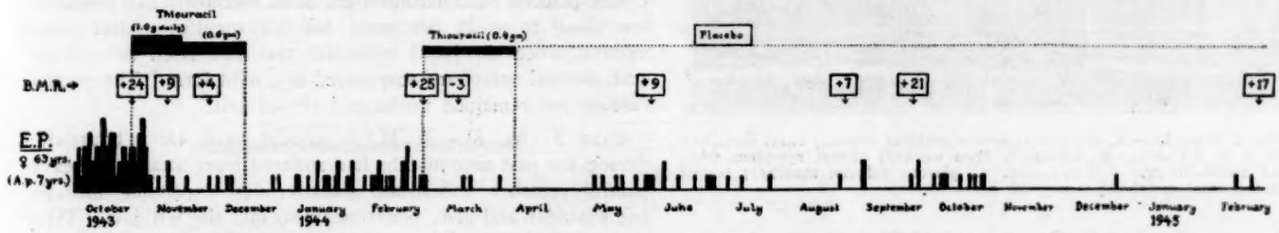


Fig. 2 (case 1).—Black columns represent anginal attacks. Their height indicates the number of attacks per day.

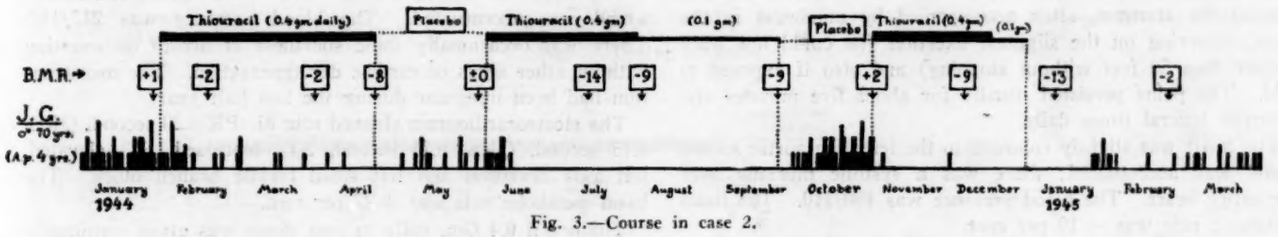


Fig. 3.—Course in case 2.

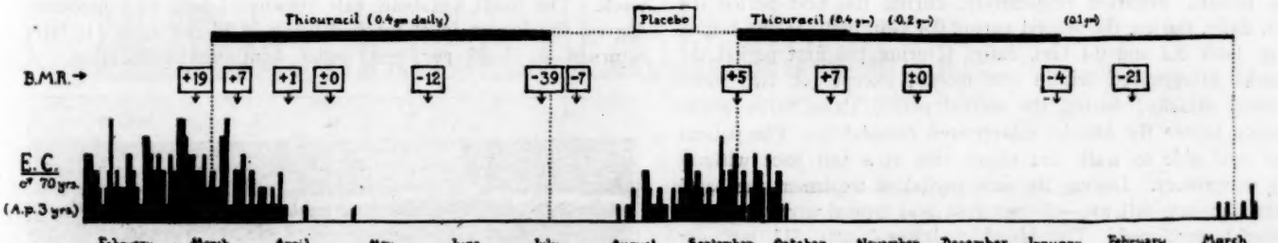


Fig. 4.—Course in case 3.

both shoulders. They were elicited by the slightest physical exertion, such as housework and walking, and furthermore by emotions and exposure to cold. At times they also occurred during bed rest.

There was a slight enlargement of the heart to the left and accentuation of the second aortic sound but no murmurs; the blood pressure was 185/102, the pulse rate 84. The basal metabolic rate was + 24 per cent.

Thiouracil was given during seven weeks, first 1.0 Gm. daily in five doses, later 0.6 Gm. daily in three doses. The anginal symptoms improved decidedly within about ten days. The basal metabolic rate fell to + 9 per cent and + 4 per cent. The patient was soon able to do her housework and to walk uphill without trouble, except for a few isolated spells of pain at increasing intervals. The electrocardiogram became practically normal within two weeks (fig. 3). Discontinuation of the medication was followed by a slowly developing but only partial relapse, while the basal metabolic rate returned to a level of + 25 per cent within eleven weeks. A second period of thiouracil medication (six weeks) caused a rapid fall of attack followed by signs of cardiac decompensation for several weeks (coronary infarction).

The heart was of normal size and shape; the blood pressure was 140/84. The electrocardiogram showed rate 61, low voltage, QRS notched, prominent $Q_3$, no upward deflection in lead 4, $T_{1,4}$ inverted, $T_{2,3}$ low. The basal metabolic rate was + 1 per cent.

The patient received three periods of thiouracil treatment of three, four and two months' duration respectively, each with a dose of 0.4 Gm. daily at the beginning, later being reduced to 0.1 Gm. daily. During the first period of treatment the anginal attacks became quite infrequent within about two weeks; during the two following periods of treatment they disappeared rapidly and almost completely. The patient was now able to walk and climb stairs without discomfort. During each period of treatment the basal metabolic rate fell 7, 14 and 11 points respectively. When it was at its lowest the face appeared slightly puffy, he complained of sleepiness and the blood cholesterol was 330 mg. per hundred cubic centimeters (Aug. 2, 1944). Reduction of the dose to 0.1 Gm. abolished the myx-

edematous features without reappearance of the anginal complaints. Each period of treatment was followed by several weeks of placebo administration without the patient's knowledge. In each instance the anginal symptoms reappeared in either partial or full relapses together with a return of the basal metabolic rate to its original level. The electrocardiogram remained unchanged throughout.

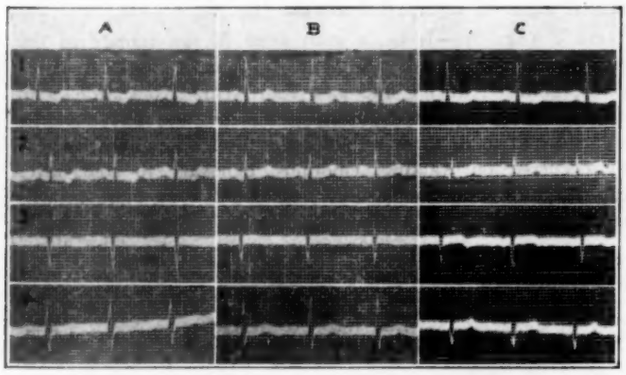


Fig. 5 (case 1).—*A*, untreated; severe anginal attacks; basal metabolic rate + 24 per cent. *B*, thiouracil (two weeks); almost symptom free; basal metabolic rate + 9 per cent. *C*, placebo (eleven months); partial relapse; basal metabolic rate + 17 per cent.

Case 3 (fig. 4).—E. C., a man aged 70, without occupation previously in good health, during the past three years had attacks of severe pain in the epigastrium and under the lower part of the sternum, often accompanied by numbness in the arms, occurring on the slightest exertion (he could not walk farther than 50 feet without stopping) and also if exposed to cold. The pains persisted usually for about five minutes and occurred several times daily.

The heart was slightly enlarged to the left; the aortic second sound was accentuated; there was a systolic murmur over the entire heart. The blood pressure was 190/110. The basal metabolic rate was + 19 per cent.

Thiouracil was given in two periods of four months' and five months' duration respectively, during the first period 0.4 Gm. daily, during the second period 0.4 Gm. daily at the beginning, later 0.2 and 0.1 Gm. daily. During the first period the attacks disappeared within one month, except for two more isolated attacks; during the second period about three weeks elapsed before the attacks disappeared completely. The patient was now able to walk and climb hills at a fast pace without any discomfort. During the first period of treatment the basal metabolic rate fell to — 39 per cent and typical myxedematous features developed. The blood cholesterol was 311 mg. per hundred cubic centimeters at this time. During the second period the basal metabolic rate fell to a minimum of — 21 per cent; the blood cholesterol was 368 mg. per hundred cubic centimeters but puffiness and sleepiness were much less pronounced with the smaller dosage.

Between the two periods of medication a nine week period of unconscious placebo intake was interpolated during which the basal metabolic rate rose rapidly although not quite to its original level, and the attacks reappeared in almost full force within three weeks.

The electrocardiogram (fig. 6) showed at first increasing pathologic changes (depression of $ST_{1, 2}$, diphasic $T_1$, flattening of $T_4$) at a time when anginal symptoms were completely absent. During the following placebo-induced relapse these changes were even more accentuated, but they gradually subsided during the second period of treatment, at the end of which the electrocardiogram was about the same as at the beginning.

Case 4 (fig. 7).—W. J. L., a man aged 68, formerly a carpenter, had previously been in good health. During the past two years a sensation of oppressing "fulness" was felt underneath the sternum once or several times daily on walking and emotions. It usually stayed on for four to five minutes and compelled the patient to stand still.

There was a moderate degree of pulmonary emphysema. The heart was slightly enlarged to the left; there was a systolic murmur over the entire heart. The blood pressure was 130/68. The electrocardiogram showed rate 67, PR 0.23 second; $T_{3, 4}$ inverted. The basal metabolic rate was — 4 per cent.

The patient received liver injections from time to time because of soreness of the tongue. There was no anemia.

Thiouracil 0.4 Gm. daily in four doses was given during three and a half months. The basal metabolic rate fell gradually to — 27 per cent. When it had reached — 14 per cent after about two weeks the anginal attacks became very infrequent and from the sixtieth day on they ceased completely. The patient was now able to walk without discomfort and to do strenuous work, such as lawn mowing and carrying wood. The blood cholesterol level was 284 mg. per hundred cubic centimeters. Under placebo administration the basal metabolic rate remained low (— 9 to — 24 per cent) for six months. After seven months, when the basal metabolic rate had risen to + 9 per cent, anginal symptoms reappeared in a mild form. The electrocardiogram remained unchanged throughout.

Case 5 (fig. 8).—R. M., a woman aged 43, a housewife, during the past nine months had suffered from attacks of heavy, painful pressure underneath the sternum, expanding into the left shoulder and arm, sometimes also into the left jaw. These were elicited by walking, emotions and cold wind and occurred several times daily, lasting several minutes.

The heart was slightly enlarged to the left. The aortic second sound was accentuated. The blood pressure was 212/112. There was occasionally some shortness of breath on exertion without other signs of cardiac decompensation. The menstruation had been irregular during the last half year.

The electrocardiogram showed rate 81, PR 0.20 second, $QRS_1$ 0.15 second, $QRS_2$ 0.11 second, $ST_1$ depressed, $ST_3$ elevated, left axis deviation and left sided bundle branch block. The basal metabolic rate was + 27 per cent.

Thiouracil 0.4 Gm. daily in four doses was given continually during five and one-half months with an interruption of one week. The basal metabolic rate responded only to a moderate degree, the lowest level reached being + 14 per cent. It later returned to + 26 per cent under continued medication. A slight improvement of the anginal symptoms was reported, beginning after five weeks of medication. The patient could walk with greater ease and on many days had no symptoms at all, but the improvement remained only partial. During a subsequent six week period of placebo administration the condition grew worse again. Two series of x-ray irradiation of

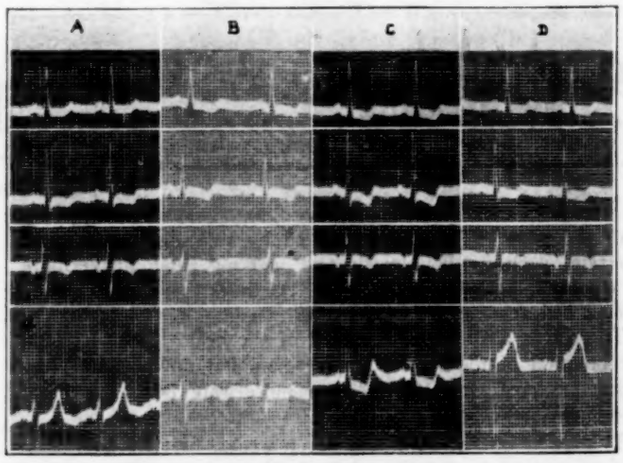


Fig. 6 (case 3).—*A*, untreated; severe anginal attacks; basal metabolic rate + 19 per cent. *B*, thiouracil (four months); symptom free; basal metabolic rate — 39 per cent. *C*, placebo (two months); complete relapse; basal metabolic rate + 5 per cent. *D*, thiouracil (four months); symptom free; basal metabolic rate — 4 per cent.

the adrenal region at a seven week interval were finally followed by an almost complete disappearance of the anginal symptoms. The electrocardiogram and blood pressure remained practically unchanged until a coronary occlusion occurred three months later.

CASE 6 (fig. 9).—J. K., a man aged 62, an employee, previously in good health, one year before examination had a coronary infarction. Since then he suffered from attacks of a "burning oppression" spreading from the epigastrium to the substernal area, sometimes accompanied by numbness of the left arm. The attacks occurred once to a few times daily on walking, emotions, after meals, rarely at rest. They lasted a few seconds to minutes.

The heart was normal to percussion and auscultation. Blood pressure was 135 systolic; the diastolic pressure was indistinct. The electrocardiogram showed rate 65, PR 0.22 second, left axis deviation, QRS notched, T flat in all leads. The basal metabolic rate was —9 per cent.

Thiouracil 0.4 Gm. daily in two doses was given during four and one-half months. The symptoms began to improve after six weeks of treatment and then disappeared completely. Physical exertion was no longer accompanied by any discomfort after one month of treatment. The basal metabolic rate had fallen to +11 per cent at this time. Pains became quite infrequent (only about once or twice a week at heavier work) and were much less intense. Walking caused only rare and little discomfort. The basal metabolic rate fell to ±0 per cent and finally, at the end of the fourth month, to —3 per cent. At this time she appeared slightly puffy and the blood cholesterol was 619 mg. per hundred cubic centimeters.

CASE 8.—G. C., a man aged 69, without occupation, who previously had been in good health, during the past four years felt an oppressing substernal pain on walking, climbing, emotions, exposure to cold, sometimes after meals. These attacks, which occurred several times per week, lasted from a few minutes to one hour. Seven months before the patient suffered a cerebral accident with temporary hemiplegia.

The heart was slightly enlarged to the left. There was a loud systolic murmur. The blood pressure was 192/88. The spinal column showed a pronounced degree of hypertrophic arthritis. The basal metabolic rate was +16 per cent. The electrocardiogram is reproduced in figure 11.

Thiouracil 0.4 Gm. daily in two doses was given during four months with an interruption of three weeks. Within about

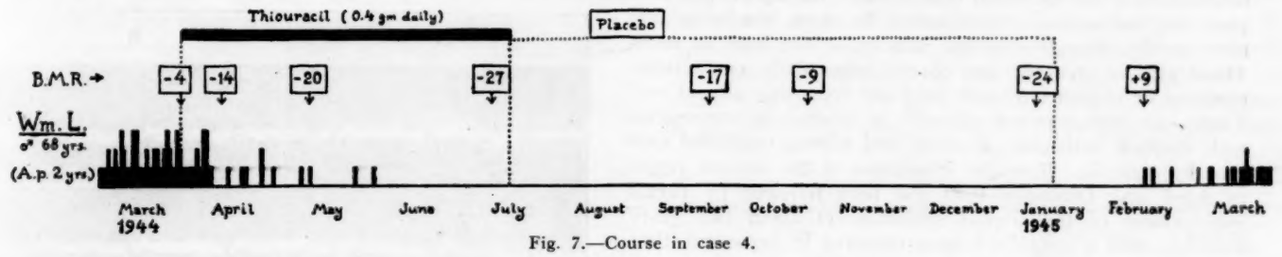


Fig. 7.—Course in case 4.

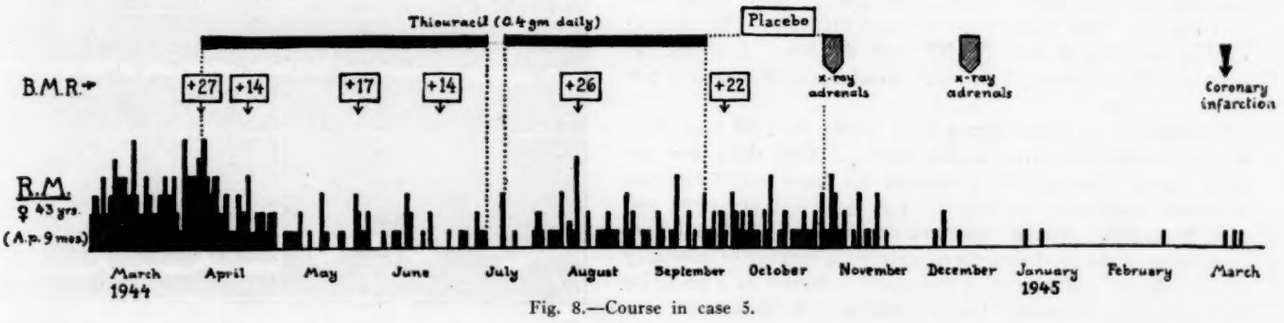


Fig. 8.—Course in case 5.

during the last two months of treatment. The basal metabolic rate began to fall only after two and one-half months. When it reached a lowest point of —19 per cent the patient appeared somewhat pasty and complained of a slight degree of sleepiness and fatigue and of an unpleasant taste "like iron." The blood cholesterol was 419 mg. per hundred cubic centimeters at this time. Replacement of thiouracil by placebos without the patient's knowledge was followed by an almost complete relapse within two weeks. The basal metabolic rate rose to +2 per cent within about three weeks. The electrocardiogram remained unchanged.

CASE 7 (fig. 10).—R. L., a woman aged 67, a housewife, who had had diabetes for the past fifteen years (daily 40 units of protamine zinc insulin), hypertension and headaches for the past six years, during the last two years had to complain of substernal pain, irradiating into the left shoulder, jaw and arm on any kind of exertion, even light housework, and furthermore on exposure to cold and on emotions. The pains occurred several times daily, lasting a few minutes to hours.

The heart was moderately enlarged to the left. The blood pressure was 225/98. The electrocardiogram showed rate 78, left axis deviation, $ST_1$ slightly depressed, $ST_3$ slightly elevated, $T_1$ inverted. The basal metabolic rate was +32 per cent. Thiouracil 0.4 Gm. in 2 doses was given daily during four months. An improvement of the anginal symptoms was noticed three weeks, when the basal metabolic rate had fallen to +7 per cent, the symptoms began to improve and the patient walked and climbed much more easily. This improvement made further progress during the entire period of treatment, and he frequently took long walks, even in very cold weather. There were still pains "from time to time" but they were no longer elicited by exertion. They were only quite mild and of a dull, aching character, which seemed to be attributable to the spinal arthritis rather than to the coronary condition. The patient stated repeatedly in writing that he felt "lots better."

The basal metabolic rate fluctuated during the first three months (+14, +7, +10, +9, +5, +12 per cent) but finally fell to —5 per cent. At this time he appeared slightly puffy and the blood cholesterol was 442 mg. per hundred cubic centimeters.

CASE 9.—R. H., a man aged 62, an undertaker, previously in good health, had during the past three years had anginal symptoms consisting of heavy substernal pressure on walking, climbing, emotions and exposure to cold wind, rarely at rest. The attacks occurred once or more daily and lasted a few minutes.

The heart was normal to percussion and auscultation. The blood pressure was 170/100. The electrocardiogram showed left axis deviation but otherwise was normal. The basal metabolic rate was —2 per cent.

Thiouracil 0.4 Gm. daily in four doses was given during three months. The anginal symptoms remained essentially unchanged, although the patient claimed that he felt "a little better with slightly diminished frequency and intensity of the attacks." The basal metabolic rate also remained practically unchanged (— 2, + 2, + 3 per cent). After three months of medication he suddenly collapsed and died at a funeral which he was conducting, obviously from coronary occlusion. No autopsy was performed.

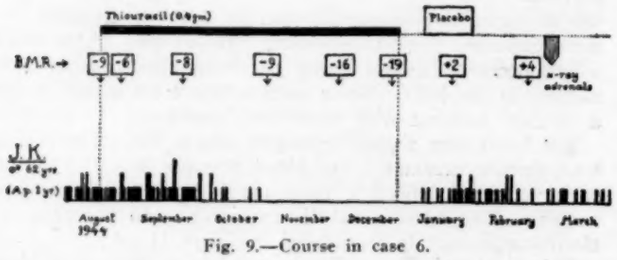


Fig. 9.—Course in case 6.

CASE 10.—M. N., a woman aged 57, a housewife, with old tuberculosis of the spine and mild diabetes, during the past four years had had attacks of pain across the chest, irradiating into both arms, lasting from a few minutes to one hour or more. These attacks occurred two to six times daily on walking, emotions or exposure to cold wind and frequently also at rest. There had been repeated episodes of cardiac decompensation with dyspnea, orthopnea, cyanosis and edema, controlled each time by digitalis. Roentgen irradiation of the adrenal region in April and December 1940 had been followed by partial improvement of the anginal symptoms of about two years' duration, until a complete relapse occurred in September 1942.

The heart was enlarged to the left. There was a systolic murmur over the entire heart. The aortic second sound was accentuated. The blood pressure was 210/120. The electrocardiogram showed rate 76, left axis deviation, $T_{1, 2}$ flat, $T_3$ inverted, $T_4$ invisible. The basal metabolic rate was + 3 per cent.

Thiouracil was given during four weeks, first 0.8 Gm. daily in four doses for three weeks, then 1.2 Gm. daily for one more week. During this treatment the basal metabolic rate remained practically unchanged (+ 3, + 1, — 1 per cent) and also the anginal attacks continued unabated. Two days before conclusion of the treatment there occurred a number of unusually severe attacks with electrocardiographic evidence of a posterior wall coronary occlusion. Death followed eight days later. No autopsy was performed.

COMMENT

Thiouracil medication proved therapeutically effective in 8 out of 10 patients with angina pectoris. In 4 cases, 3 of which can be classified as severe, the

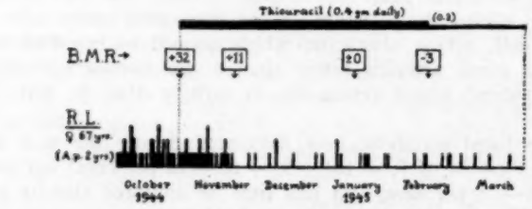


Fig. 10.—Course in case 7.

symptoms disappeared entirely during the treatment. When the drug was replaced by placebo tablets without the patient's knowledge, partial or complete relapses occurred within a matter of weeks or months in these 4 cases.

Definite improvement regarding the frequency and intensity of the anginal symptoms occurred in 3 cases. In 1 of them the treatment was followed by placebo administration, leading to a partial relapse.

One patient was only slightly improved, but two subsequent series of roentgen irradiations of the adrenal region brought the symptoms to almost complete disappearance.

Two patients with severe angina pectoris died from coronary occlusion, while the treatment was still under way, without having experienced an improvement of their symptoms.

The dosage ranged between 1.2 Gm. (1 case) and 0.4 Gm. per day in divided doses at the beginning of the treatment to 0.1 Gm. daily as a maintenance dose.

The onset of subjective improvement was reported after ten days to six weeks of medication. If thiouracil was given in a second or third period following placebo-induced relapses, improvement and disappearance of symptoms occurred more rapidly.

A significant decrease of the basal metabolic rate was observed in the 7 decidedly or completely improved patients, rather closely paralleling the diminution or disappearance of the anginal symptoms. No significant lowering of the basal metabolic rate occurred in

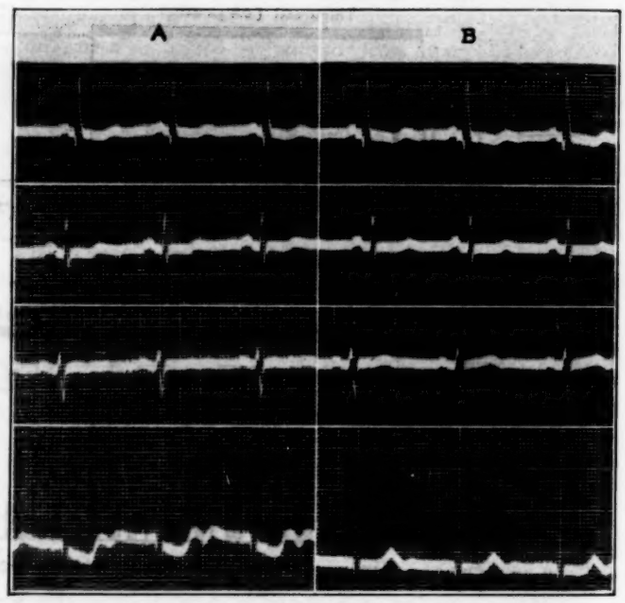


Fig. 11 (case 8).—*A*, untreated; anginal symptoms on walking and other effort; basal metabolic rate + 16 per cent. *B*, thiouracil (four months); considerably improved; no more pain on walking; basal metabolic rate — 5 per cent.

the 2 nonresponding patients who died, and only a moderate and temporary fall was observed in the 1 patient who was only slightly improved.

Maximum improvement was reached when the basal metabolic rate had fallen 7 to 27 points below its original level, as shown in the table. Relapses occurred simultaneously with a return of the basal metabolic rate toward its pretreatment level. In case 4 the basal metabolic rate remained for six months far below the pretreatment level and there was freedom from symptoms during this entire period. In case 2 analogous developments required only a few days.

The initial basal metabolic level at the time of introduction of the thiouracil treatment had no apparent influence on the efficacy of the medication. It ranged between + 32 and — 9 per cent. In none of the 10 patients were there any indications of hyperthyroidism. High basal metabolic levels are not unusual in hypertensive patients (e. g. patients 1, 5 and 7). They are probably of hypothalamic origin.[62]

62. Raab, Wilhelm: Hypermetabolic Hypertension: A Syndrome of Central Nervous Origin, to be published.

Fully developed myxedema resulted in case 3; in cases 2, 6, 7 and 8 there was some puffiness of the face, in 2 of them combined with sleepiness, when the basal metabolic rate had reached its lowest level. These phenomena disappeared spontaneously within one to two weeks after discontinuation or reduction of the thiouracil medication. The blood cholesterol was elevated during the hypothyroid episodes.

The electrocardiogram was rapidly normalized in case 1 and remained so for about six months of placebo administration until the basal metabolic rate returned to its former level. A partial normalization of the electrocardiogram occurred also in case 8 together with clinical improvement. In case 13, on the other hand, the pathologic changes of the electrocardiogram became even more pronounced during the first thiouracil period than before treatment. They reached a maximum during a severe relapse under placebo administration but reverted to the original degree when the patient became again symptom free during a second thiouracil period. In the other cases no significant changes of the electrocardiogram were noted.

The behavior of the blood pressure was uncharacteristic.

No untoward side effects of the thiouracil medication were observed in any case.

bolic rate and symptomatic response is the fundamental involvement of even the normal thyroid function in the mechanism of a probably large group of angina pectoris cases. That this involvement consists essentially of a sensitization of the heart muscle to the anoxiating action of epinephrine and probably also of sympathin originating in the heart itself is suggested by many clinical and experimental facts as outlined in the introduction.

Failure of anginal symptoms to respond to thiouracil, as in cases 9 and 10, may be due to the rather wide individual differences regarding the effect of thiouracil on the human thyroid gland as described by Astwood.[59] On the other hand, even complete absence of thyroid function, as in total thyroidectomy, does not always abolish the anginal symptoms (Claiborne and Hurxthal [4] and others). The degree of coronary stenosis, of the intensity of epinephrine discharges and other factors may be responsible for these differences of therapeutic results. In 1 case that I observed anginal symptoms persisted after total thyroidectomy despite the development of myxedema. Two others with spontaneous myxedema also showed typical angina pectoris.

Elaboration of an ideal dosage of thiouracil both for initial treatment of angina pectoris and for maintenance of an established improvement will require further pro-

*Observations in Ten Cases*

| Case No. | Age | Sex | Blood Pressure, Mm. Hg | Duration of Angina Pectoris, Years | Severity of Angina | Basal Metabolic Rate, % | Degree of Response to Thiouracil | Onset of Improvement | Diminution of B. M. R. at Time of Maximum Improvement * | Maximum Duration of Improvement After Discontinuation of Thiouracil |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 63 | ♀ | 185/102 | 7 | Severe | +24 | ++ | 10 days | —27 | 11 months |
| 2 | 70 | ♂ | 140/ 84 | 4 | Medium | + 1 | +++ | 2 weeks | —15 | 2 months |
| 3 | 70 | ♂ | 190/110 | 3 | Severe | +19 | +++ | 1 month | —19 | 1 month |
| 4 | 68 | ♂ | 130/ 68 | 2 | Severe | — 4 | +++ | 2 weeks | —23 | 7 months |
| 5 | 43 | ♀ | 212/112 | ¾ | Severe | +27 | ± | 5 weeks | —13 | ..... |
| 6 | 62 | ♂ | 135/ ? | 1 | Medium | — 9 | +++ | 6 weeks | — 7 | 2 weeks |
| 7 | 67 | ♀ | 225/ 98 | 2 | Medium | +32 | ++ | 1 month | —21 | ..... |
| 8 | 69 | ♂ | 192/ 88 | 4 | Medium | +16 | ++ | 3 weeks | — 9 | ..... |
| 9 | 62 | ♂ | 170/100 | 3 | Severe | — 2 | — | ..... | .... | ..... |
| 10 | 57 | ♀ | 210/120 | 4 | Severe | + 3 | — | ..... | .... | ..... |

* Points.

The therapeutic results obtained with thiouracil so far are similar to those described after thyroidectomy by Blumgart and his associates,[2] Levine and Eppinger [3] and others. These workers found a basal metabolic level of about —20 per cent most favorable regarding prevention of both anginal symptoms and of troublesome myxedematous features. The prompt disappearance of myxedematous phenomena with discontinuation or reduction of thiouracil is one of the advantages of this reversible "functional thyroidectomy" over the irreversible surgical procedure, which often requires substitutive thyroid medication.

The coincidence of symptomatic response and of response of the basal metabolic rate to thiouracil was quite striking. However, this cannot be considered as proof of the conception that the presence or absence of anginal symptoms is directly determined by the rate of systemic oxygen consumption. This conception has been questioned also in regard to the effect of thyroidectomy by Eppinger and Levine [8] and by Scherf.[6] According to Leblond and Hoff [63] the effect of thyroxine on the heart is a direct one and not the consequence of general metabolic stimulation.

The only fact which can be concluded from the approximate parallelism of changes in the basal metalonged observations. From the cases reported it would seem that a dosage quite similar to that in hyperthyroidism will be adequate: 0.4 Gm. daily for a few weeks or months followed by a maintenance dose of 0.2 or 0.1 Gm. daily over longer periods of time and eventually tentative discontinuation of the drug. Doses larger than 0.6 Gm. per day should be avoided in view of the possibility of untoward side effects as described in the literature on thiouracil.

Whether or not the elevation of the blood cholesterol level which is likely to result from thiouracil medication has to be regarded as a serious disadvantage, considering a possible enhancement of coronary sclerosis, can be decided only on the grounds of much larger and prolonged series of observation. According to Shaffer [64] a significant role of cholesterolemia in the origin of coronary sclerosis is doubtful.

The objection usually raised against claims of therapeutic results in angina pectoris, that they are "psychogenic" or "imaginary," cannot be upheld against the results of thiouracil treatment in view of the clear-cut relapses occurring under unconscious placebo medication.

The therapeutic efficacy of thiouracil in angina pectoris makes this drug appear as a valuable and preferable substitute for thyroidectomy, and it constitutes a

63. Leblond, C. P., and Hoff, H. E.: Comparison of Cardiac and Metabolic Actions of Thyroxine, Thyroxine Derivatives and Dinitrophenol in Thyroidectomized Rats, Am. J. Physiol. **141**: 32, 1944.

64. Shaffer, C. F.: The Nutritional Role of Cholesterol in Human Coronary Arteriosclerosis, Ann. Int. Med. **20**: 948, 1944.

further step in the clarification of the pathogenesis of angina pectoris as a phenomenon of hormonal chemical interference in myocardial metabolism.

All prolonged therapeutic successes which were reported, up to the present, as being achieved in angina pectoris by therapeutic measures influencing the endocrine system can be explained as being due to a diminution of the acutely anoxiating effect of epinephrine and sympathin on the myocardium whose blood supply is curtailed by coronary sclerosis:

1. Thyroidectomy decreases the sensitivity of the heart to epinephrine (Sawyer and Brown,[52] Eppinger and Levine,[8] Shambaugh and Cutler [9]).

2. Thiouracil, by suppressing the formation of thyroid hormone, acts in the same manner, as evidenced by experiments on animals and man.[65]

3. Roentgen irradiation of the adrenal region (Raab,[22] Hutton,[44] Hadorn,[45] Schittenhelm,[46] Lippross,[47] Raab and Soule [48]) abolishes the abnormally intense discharges of epinephrine and related compounds which are a characteristic of angina patients.[25]

4. Testosterone propionate (Hennsge,[66] Pick,[67] Arndt,[68] Walker,[69] Bonnell, Pritchett and Rardin,[70] Lesser,[71] Hamm,[72] McGavack [73]) normalizes the myocardial metabolic changes which follow on castration (Schumann [74]) and which seem to be due to the presence of increased amounts of epinephrine in the heart muscle.[18] They are qualitatively identical with those elicited by epinephrine (Schumann [74]).

The traditional but inadequate explanations of angina pectoris as a manifestation of acute myocardial anoxia caused by "overwork" or "coronary spasm" served their purpose as long as nothing was known about myocardial metabolism and the fundamental role of neurohormonal factors in its physiologic and pathologic aspects. These factors are becoming increasingly apparent and are likely to make some of the customary mechanistic hypotheses obsolete.

SUMMARY

Treatment with thiouracil proved effective in 7 out of 10 patients with angina pectoris, 4 of whom became entirely symptom free during the treatment. One patient was only slightly improved. Two patients remained unimproved and died from coronary occlusion.

Clinical improvement coincided rather closely with the fall of the metabolic rate and failed to occur in those patients whose basal metabolic rate did not decrease.

Replacement of thiouracil by placebos without the patient's knowledge was followed by a partial or complete recurrence of the anginal symptoms, coinciding with a return of the basal metabolic rate toward its former level within ten days to seven months following discontinuation of the thiouracil medication.

The thyroid hormone, even in physiologic amounts, sensitizes the heart muscle to the anoxiating toxic action of epinephrine. Thiouracil exerts an opposite, heart-protecting effect, obviously through suppression of thyroid hormone formation.

In view of these and many other experimental and clinical facts the efficacy of "functional thyroidectomy" through thiouracil is ascribed to a diminution of myocardial sensitivity to heart-anoxiating, angina-producing epinephrine and sympathin discharges.

65. Raab, footnotes 55 and 60.
66. Henssge, E.: Die Beseitigung vasomotorischer Störungen durch Testoviron und eine vergleichende Darstellung über die Wirkung männlicher Hormone, Aerztl. Kor. **21**: 537, 1937.
67. Pick, R.: Die hormonale Behandlung der Keimdrüseninsuffizienz beim Mann mit Berücksichtigung des synthetischen Testosteron-propionats Perandren, Med. Klin. **34**: 17, 1938.
68. Arndt, H.: Zur Therapie extragenitaler Störungen mit Sexualhormonen, Wien. med. Wchnschr. **89**: 222, 1939.
69. Walker, T. C.: Use of Testosterone Propionate and Estrogenic Substance in Cardiovascular Disease, M. Rec. & Ann. **34**: 667, 1940.
70. Bonnell, R. W.; Pritchett, C. P., and Rardin, T. E.: Treatment of Angina Pectoris and Coronary Artery Disease with Sex Hormones, Ohio State M. J. **37**: 554, 1941.
71. Lesser, N. A.: Treatment of Angina Pectoris with Testosterone Propionate, New England J. Med. **226**: 51, 1942; **228**: 185, 1943.
72. Hamm, L.: Testosterone Propionate in the Treatment of Angina Pectoris, J. Clin. Endocrinol. **2**: 325, 1942.
73. McGavack, T. H.: Angina-like Pain: A Manifestation of the Male Climacterium, J. Clin. Endocrinol. **3**: 71, 1943.
74. Schumann, H.: Der Einfluss der männlichen Sexualhormone auf den Glykogen-, Phosphagen- und Adenylpyrophosphatgehalt des Herzmuskels, Klin. Wchnschr. **18**: 925, 1939.

## WHY USE SPINAL ANESTHESIA?

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Many reasons have been advanced for using spinal anesthesia, ranging from pure convenience to increased safety for the patient. This type of anesthesia has been utilized for every type of operation, from removal of warts and ingrown toenails to craniotomy. As with other forms of anesthesia, too much emphasis has been placed on the selection of the agent and method rather than on the skill and experience of the one responsible for the administration.

This form of anesthesia is so generally and successfully employed for surgery of the lower part of the abdomen and the extremities that its use for surgery in these areas will not be considered in this paper. On the other hand, the utilization of spinal anesthesia for surgery of the chest, head and neck is considered to be fraught with too many dangers to allow for its general use. This discussion, therefore, will be limited to an attempt to give an answer to the question "Why use spinal anesthesia for upper abdominal surgery?" Irrespective of how many other reasons or excuses may be advanced for the use of spinal anesthesia for surgery in the upper part of the abdomen, the most important one is that a completely successful spinal anesthesia gives working conditions in the abdomen unexcelled and rarely equaled by other methods. Usually all other reasons play a secondary role to this one. Assuming this statement to be correct and that next to the elimination of the actual pain of surgery, with as little disturbance of physiologic processes as possible, the most important function of any anesthesia is to facilitate the work of the surgeon, it would seem to follow naturally that, unless there were important disadvantages and deleterious side effects, spinal anesthesia would be the natural choice for practically all abdominal surgery.

Unfortunately there are several disadvantages and undesirable side effects of spinal anesthesia that, until means could be devised for circumventing or nullifying them, made the selection of this method for upper abdominal surgery often unwise. Many of these objections apply to the use of spinal anesthesia in general, while others have a more special significance when the anesthesia is intended for operations in the upper part of the abdomen.

The disadvantages of spinal anesthesia which must be overcome before it can be employed with uniform success for surgery in the upper part of the abdomen are (1) difficulty in obtaining anesthesia sufficiently high to permit work in this area without discomfort to the patient and with adequate muscular relaxation, (2) insufficient duration of anesthesia necessitating a change

From the Department of Anesthesia, the Lahey Clinic.
Read before the Section on Anesthesiology at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 14, 1944.

to a less satisfactory method during the course of the operation, (3) respiratory depression, (4) circulatory depression, (5) nausea, retching and vomiting during operation and (6) psychic objection on the part of the patient and even of the surgeon and anesthetist to the patient being awake during the operation.

The first three disadvantages and to some extent the fourth are closely related to the distribution of the spinal anesthetic agent in the spinal canal. The height or cephalad distribution of anesthesia is obviously a result of the presence of the agent in the spinal canal at the level from which the corresponding nerve roots arise. Frequently, however, it is not appreciated that the duration of spinal anesthesia at a certain level is to a great extent a direct function of the concentration of the agent. In order to have long lasting upper abdominal anesthesia, the maximum concentration of the agent must be along the nerve roots supplying the upper part of the abdomen and not at the spinal puncture site in the lumbar area. Another factor of great importance is that all of the nerve supply to the abdomen

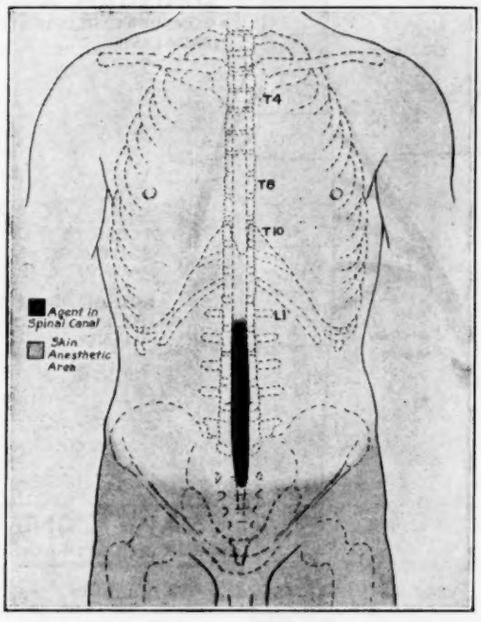


Fig. 1.—Anesthetic level necessary for perineal and lower extremity surgery.

arises in the thoracic segments of the spinal cord. This means that there is almost invariably some impairment of lower intercostal muscle activity with spinal anesthesia for abdominal surgery. Of course, the higher the anesthesia the more intercostal muscles are impaired. If the agent progresses cephalad to the first thoracic segment in sufficient concentration, all intercostal muscles become paralyzed. Paralysis of the diaphragm will ensue if the motor nerves are involved as high as the fourth cervical segment.

A review of some of the anatomic factors involved in the distribution of spinal anesthesia may be helpful in appreciating the problems associated with distributing the major portion of an anesthetic agent on the nerve roots to the upper part of the abdomen and at the same time stopping the agent short of respiratory paralysis. Figures 1, 2, 3 and 4 are representations of the distribution of the spinal anesthetic agent in the spinal canal with the corresponding sensory surface distribution of anesthesia. In order to have anesthesia to the groin, the anesthetic agent must be as high as the first lumbar segment (fig. 1). If the agent is advanced cephalad to the tenth thoracic segment, surface anesthesia will be present to the umbilicus (fig. 2). This level would permit surgery on the perineum, anus, extremities and superficial operations on the lower part of the abdomen.

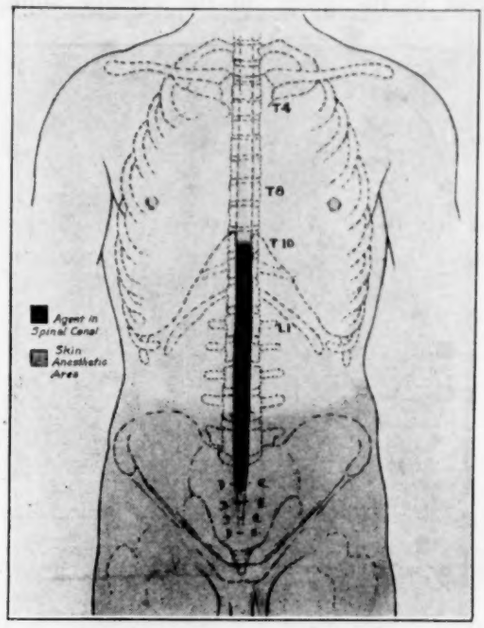


Fig. 2.—Anesthetic level necessary for superficial operations in the lower part of the abdomen.

With sensory anesthesia no higher than this, intra-abdominal operations could be performed only in the lower part of the abdomen and then without abdominal exploration or tension on the viscera. With the agent

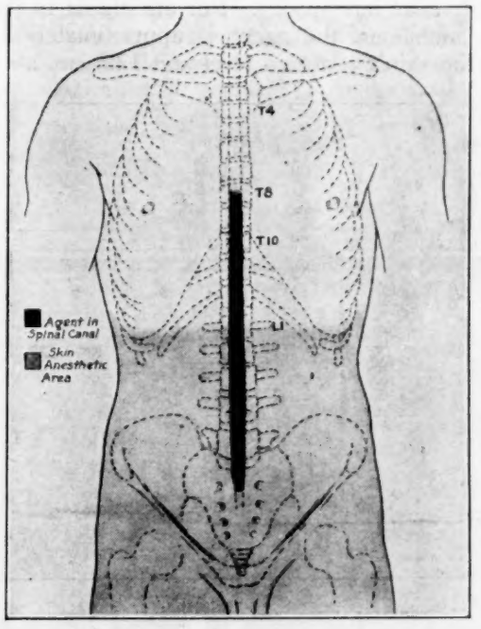


Fig. 3.—Anesthetic level necessary for midabdominal and lower abdominal surgery.

at the level of the seventh thoracic segment, the upper border of sensory anesthesia is at the costal margin (fig. 3). This is still not high enough to permit operations in the upper part of the abdomen or complete abdominal exploration. Completely satisfactory anesthesia for operations such as hysterectomy or appen-

dectomy should not be lower than this. Satisfactory spinal anesthesia for upper abdominal surgery cannot be obtained until the agent has progressed cephalad to approximately the fourth thoracic segment. This gives surface anesthesia to the nipple line (fig. 4). To obtain anesthesia to the groin, in the average adult male

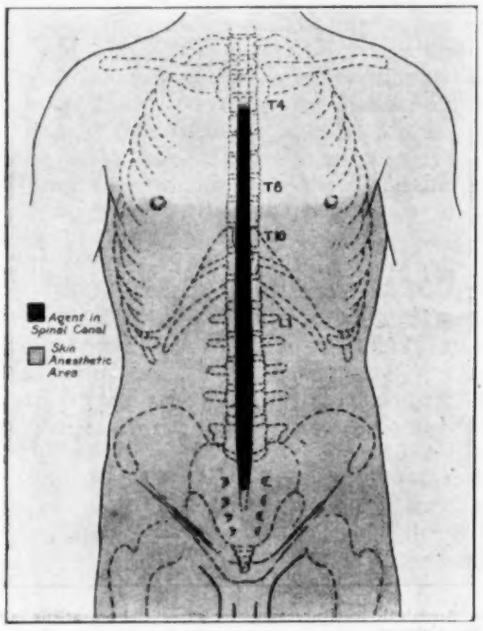


Fig. 4.—Anesthetic level necessary for complete abdominal exploration and upper abdominal surgery.

patient the anesthetic agent must reach a level in the spinal canal approximately 18 cm. above the sensory skin level and 7.5 cm. above the usual site of injection (third lumbar interspace). For anesthesia to the level of the umbilicus, the agent is approximately 15 cm. above the skin anesthesia level and 12.5 cm. above the

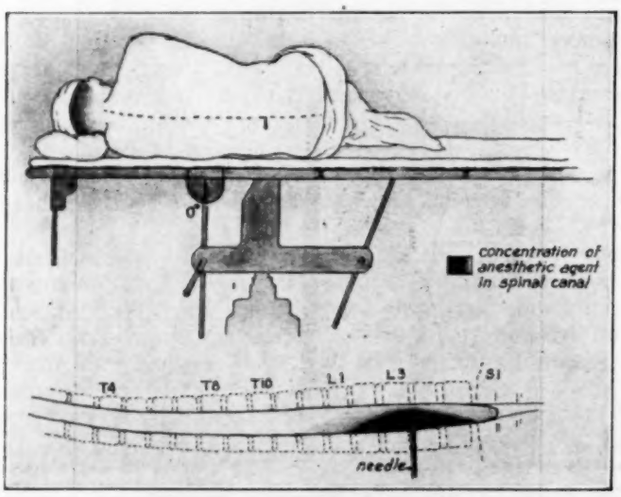


Fig. 5.—Position of patient for injection of anesthetic agent, with diagram illustrating distribution of the anesthetic agent in the spinal canal immediately following injection, when diffusion or volume technic is employed.

site of injection. If, however, we wish anesthesia to the nipple line for upper abdominal surgery, the agent must travel 26 cm. from the site of injection and will be 7 cm. above the superficial sensory level.

With surface anesthesia to the nipple line, the agent is present in the spinal canal approximately 14 cm. from that level, which may result in respiratory paralysis. This represents the average distance from the fourth thoracic segment to the fourth cervical segment (origin of the phrenic nerve) and leaves only the upper three or four intercostal muscles unaffected (fig. 6).

There are, of course, many factors that influence the distance an anesthetic agent will progress cephalad in the spinal canal. The site of injection often is thought to play an important part in the height of spinal anesthesia. While this factor does play a minor role, it is relatively unimportant as long as the injection is made anywhere in the lumbar area. Other factors of importance are the volume of solution injected, the speed of injection, the amount of barbotage employed, diffusion and, finally, the influence of gravity when there is a difference between the specific gravity of the anesthetic

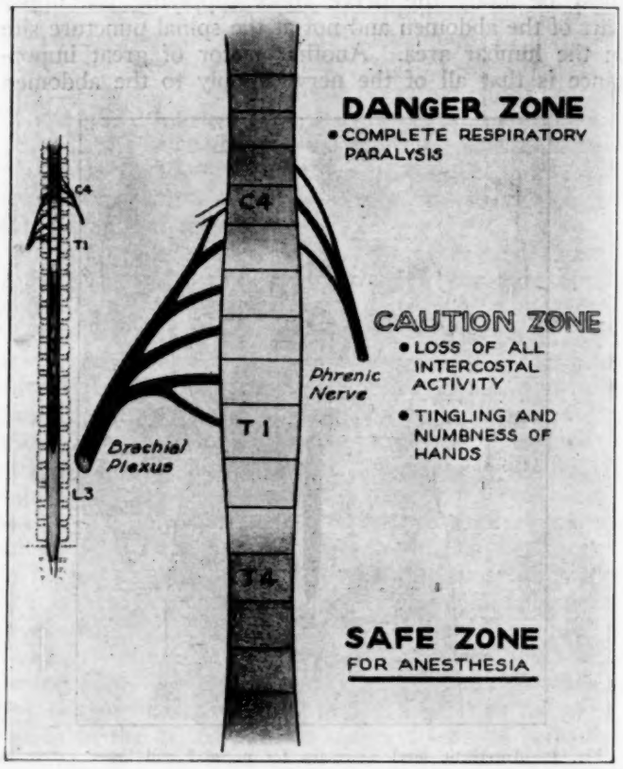


Fig. 6.—Diagrammatic section of spinal canal. Note proximity of fourth thoracic segment (level necessary for satisfactory upper abdominal surgery) to origin of phrenic nerve.

solution and the spinal fluid. In addition, there are anatomic factors such as spinal curves and arachnoidal adhesions which may influence the distribution of the anesthetic agent in the spinal canal.

It is unfortunate that the factor usually depended on primarily for distribution of the anesthetic agent in the spinal canal is simple diffusion, a process over which little control can be exercised. When a spinal anesthetic mixture of approximately the same specific gravity as spinal fluid is employed or when the patient is kept level during and immediately following the injection of the agent, diffusion is the factor playing the greatest part in its distribution. However, volume and rate of injection are factors that must be considered. In any event the maximum concentration is at the site of injection, that is, in the lumbar area, which is the level from which the nerves to the lower extremities arise. It follows that the concentration is in inverse ratio to the distance from the site of injection. The

result is longer lasting anesthesia in the extremities, with a gradual decrease in the duration of anesthesia toward the head. Figure 5 is a representation of what is assumed to be the distribution of the agent in the spinal canal during and immediately following its injection, while figure 7 represents the later distribution of the agent with corresponding surface areas of anesthesia where a diffusion technic is employed.

It has been shown experimentally that a fluid with a higher specific gravity can be fairly accurately distributed in a glass tube containing fluid of a lower specific gravity. Clinical experience in employing this principle for more than 15,000 patients has shown that the spinal canal and its contained fluid can be treated almost as though it were a test tube. By maintaining a constant tilt of the operating table (head down from the horizontal) and using an anesthetic mixture of a constant specific gravity, always heavier than the spinal fluid, and a constant rate of injection in the same lumbar interspace, the height of anesthesia can be fairly accurately determined by employing only one variable. This variable is the time that the table and patient are kept in the head down position. By this

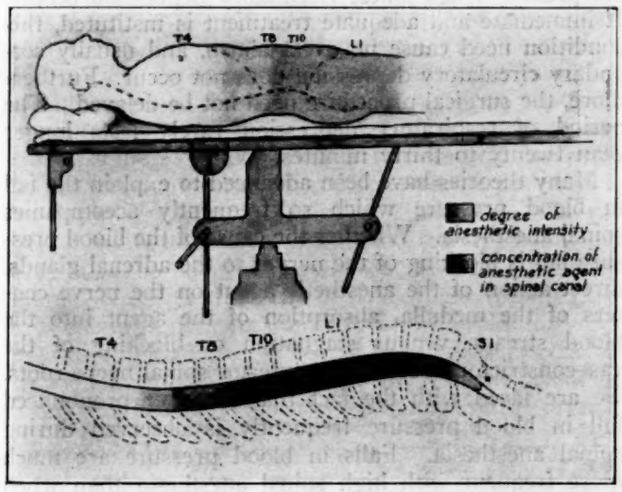


Fig. 7.—Distribution of the anesthetic agent in the spinal canal with corresponding areas of anesthesia intensity after anesthesia has been established, when diffusion or volume technic is employed.

method the bulk of the anesthetic solution can be placed at the level desired to give the maximum concentration on the nerve roots supplying the area in which the operation is to take place. For exploration over the dome of the liver it must be as high as the fourth thoracic segment, and for operations on the stomach and gallbladder there must be a rather high concentration of the anesthetic agent as far up as the fifth or sixth thoracic segment.

If an innoxious substance with a fairly high specific gravity compared with that of spinal fluid (specific gravity 1.003 to 1.010) is mixed with the anesthetic solution, a mixture is obtained that is heavy enough to allow the agent to be carried cephalad by gravity more or less as a mass. Ten per cent dextrose with a specific gravity of 1.039 is a satisfactory substance for this purpose. A technic for obtaining anesthesia suitable for upper abdominal surgery employing these principles has been devised.[1] The desired dose of pontocaine (10 to 20 mg.) is made up to a 1 per cent solution in isotonic solution of sodium chloride. To this is added 1.5 parts of 10 per cent dextrose. The specific gravity of this mixture is now 1.027. This mixture is injected slowly (0.25 cc. per second) in the third lumbar interspace with the patient on the side. Prior to starting the injection, the table is turned in

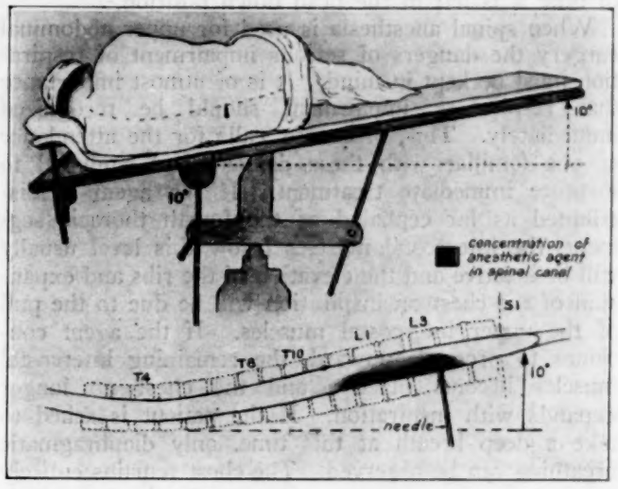


Fig. 8.—Position of patient for injection of anesthetic agent, with diagram illustrating the distribution of the agent in the spinal canal during and immediately following the injection, when hyperbaric gravity technic is employed.

the head down position, 10 degrees from the horizontal, with the patient's head elevated to raise the cervical and upper thoracic spine. The patient immediately is turned on the back, and the height of anesthesia should be tested almost constantly until the desired level is obtained. The level of anesthesia usually will be to the nipple line (fourth thoracic segment) in one to two minutes. The patient should not be left in the head down position longer than one minute unless tests show the anesthetic level to be lower than the xiphoid process (sixth thoracic segment). An accurate determi-

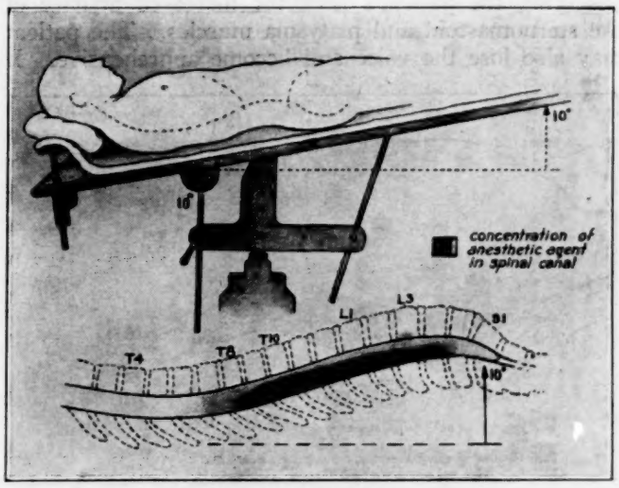


Fig. 9.—Position of patient for obtaining desired level of anesthesia, with diagram illustrating later distribution of the agent in the spinal canal, when hyperbaric gravity technic is employed.

nation of the height of anesthesia should be repeatedly obtained as long as the table is in the head down position and for several minutes thereafter. Figures 8 and 9 represent attempts to demonstrate graphically the course of a hyperbaric (heavier than spinal fluid) anesthetic solution in the spinal canal when the gravity technic is employed.

1. Sise, L. F.: Pontocaine-Glucose Solution for Spinal Anesthesia, S. Clin. North America **15**: 1501-1511 (Dec.) 1935; **16**: 1707-1711 (Dec.) 1936. Nicholson, M. J.: Pontocaine-Glucose Solution for Spinal Anesthesia, ibid. **20**: 639-646 (June) 1940. Schuhmacher.[2]

Figure 10 represents diagrammatically the distribution of a spinal anesthetic agent in greatest concentration in the upper and midthoracic segments, with corresponding areas of intensity of surface anesthesia.

This technic can be varied for lower levels of anesthesia by changing the tilt of the table or the length of time it is left in the head down position.

When spinal anesthesia is used for upper abdominal surgery the dangers of serious impairment of respiration must be kept in mind. It is of utmost importance that respiratory impairment should be recognized immediately. This, of course, calls for the attendance of one familiar with these dangers and equipped to institute immediate treatment. If the agent is distributed as far cephalad as the fourth thoracic segment, the intercostal muscles below this level usually will be inactive and the elevation of the ribs and expansion of the chest on inspiration will be due to the pull of the upper intercostal muscles. If the agent continues to progress upward, the remaining intercostal muscles become inactive and the chest no longer expands with inspiration. If the patient is asked to take a deep breath at this time, only diaphragmatic breathing can be observed. The chest remains entirely motionless or may even retract on inspiration. This is one of the earliest and most important warning signs that the anesthesia is going too high. At this time or soon afterward the patient may complain of numbness or tingling in the hands. This is, of course, due to involvement of the roots of the brachial plexus (fig. 6). Figure 11 illustrates the normal position assumed by the chest and abdomen on inspiration, as well as their position after complete intercostal paralysis. If the fourth cervical nerve is involved, the diaphragm becomes paralyzed with complete respiratory arrest. Before the phrenic nerves are completely involved, the conscious patient attempts to increase the size of the chest cavity by using the accessory muscles of respiration. This can be detected readily by observing the patient's neck for increased activity of the sternomastoid and platysma muscles. The patient may also lose the voice and become apprehensive. If

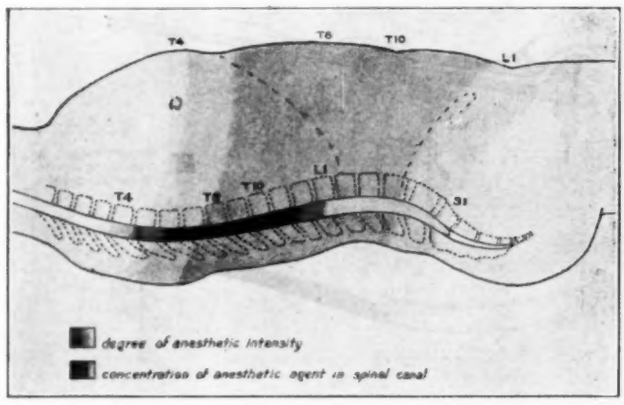


Fig. 10.—Distribution of the anesthetic agent in the spinal canal with corresponding areas of anesthesia intensity after anesthesia has been established, when hyperbaric gravity technic is employed.

unrelieved, this condition may lead to hypoxia, circulatory collapse and death. The treatment is obvious. It consists in the administration of oxygen with some mechanical assistance to inspiration if there is inadequate respiratory exchange. This assistance is absolutely essential if there is complete respiratory arrest. The assistance to respiration can best be accomplished by administering oxygen from a gas machine and exerting rhythmic pressure on the rubber breathing bag coincidental with each attempt at inspiration or about sixteen times per minute. Obviously the establishment of a free and unobstructed airway is imperative. Respiratory stimulants are not indicated and neither

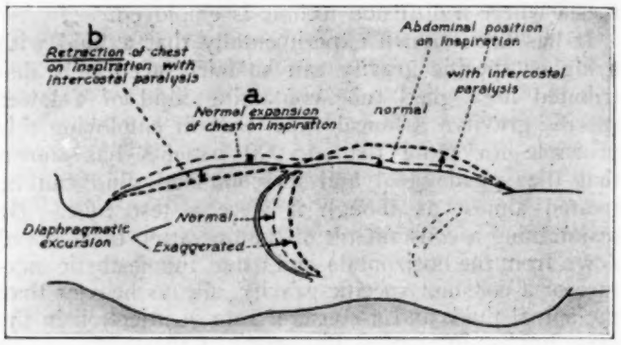


Fig. 11.—Position assumed by chest and abdomen with (*a*) normal inspiration and (*b*) inspiration after complete intercostal paralysis. Note exaggerated diaphragmatic and abdominal motion.

are pressor drugs unless circulatory depression occurs. If immediate and adequate treatment is instituted, this condition need cause no great alarm, and usually secondary circulatory depression does not occur. Furthermore, the surgical procedure need not be delayed. The period of respiratory depression rarely lasts longer than twenty to thirty minutes.

Many theories have been advanced to explain the fall in blood pressure which so frequently accompanies spinal anesthesia. Whether the cause of the blood pressure fall is blocking of the nerves to the adrenal glands, direct action of the anesthetic agent on the nerve centers of the medulla, absorption of the agent into the blood stream, venous stagnation or blocking of the vasoconstrictor fibers in the anterior spinal nerve roots, we are faced with the fact that a rather pronounced fall in blood pressure frequently is observed during spinal anesthesia. Falls in blood pressure are much more frequent with high spinal anesthesia than when the anesthesia is confined to the lower part of the abdomen. This hypotension may be alarming and should always be considered unphysiologic. Surgical manipulation in the abdomen, of course, plays a part in the production of blood pressure fall, and severe circulatory depression always follows unrelieved respiratory depression. While a severe blood pressure fall often is not observed with high spinal anesthesia, one should always remember that such an occurrence may be manifested independent of the operative procedure and without any demonstrable respiratory depression. The routine use of 50 to 75 mg. of ephedrine intramuscularly a few minutes prior to the induction of spinal anesthesia is a valuable safeguard against circulatory depression. Many of the pressor drugs have been employed successfully to combat blood pressure falls which in spite of prophylactic ephedrine have reached a level low enough to require treatment. Epinephrine and neosynephrine are effective in raising blood pressure; however, these drugs often have a rather transient effect and may disturb cardiac rhythm. Intramuscular ephedrine alone is usually effective but is somewhat slow in action. An extract of the posterior part of the pituitary gland (pitressin) is an effective blood pressure raising drug and is usually prompt in action. The fact that this drug may constrict the coronary

arteries and decrease the blood supply to the heart must be borne in mind. This danger may be minimized if it is combined with ephedrine. A combination of 5 units of pitressin and 25 mg. of ephedrine intramuscularly has proved very satisfactory in the treatment of blood pressure falls due to spinal anesthesia.[2] The response is usually prompt and well sustained, and one dose as a rule is sufficient. One fourth to one third of this dose can be given intravenously in the presence of a severe fall in pressure. The heart rate and rhythm usually are changed but little if any with this combination.

Nausea, retching and vomiting are frequent annoying complications of spinal anesthesia. No single factor is responsible for this complication, and probably more than one factor plays a part. The presence of the anesthetic agent in sufficient quantity in the fourth ventricle in dogs will produce vomiting. This may be the cause of vomiting under spinal anesthesia in some instances. Reduced blood pressure with tissue hypoxia, direct action of the drug on centers in the fourth ventricle through the circulation, traction reflexes in the abdomen and side effects of preoperative narcotics may all be factors contributing to nausea and vomiting under spinal anesthesia. If this complication is more than a momentary disturbance, the patient should be rendered unconscious by the use of an inhalation agent such as cyclopropane or nitrous oxide or by the intravenous administration of an anesthetic agent such as pentothal sodium. This enables the surgical procedure to proceed uninterrupted and relieves the patient from an uncomfortable and disturbing experience. The danger of vomitus being aspirated into the trachea should always be borne in mind when a general anesthetic is administered for the relief of nausea and vomiting.

Sometimes patients object to being awake during an operation, although not nearly as often as is generally thought. An additional dose of morphine intravenously after the patient is in the operating room prior to

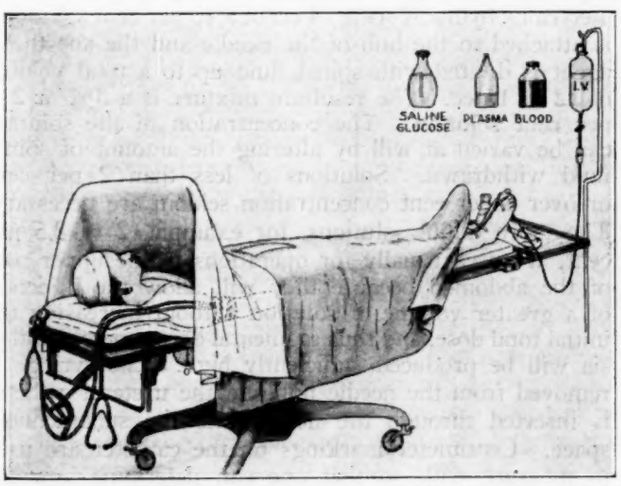


Fig. 12.—Patient ready for operation under spinal anesthesia. Note blood pressure cuff and constant intravenous drip in place (needle in saphenous vein). Supportive fluids and supplementary intravenous agents available.

induction of spinal anesthesia often allays apprehension and nervousness. There is no reason why any patient who objects to being awake during an operation cannot have the comfort of being asleep and at the same time not be denied the advantages of spinal anesthesia. The administration of cyclopropane in concentrations only high enough to maintain unconsciousness is a valuable adjunct to spinal anesthesia. If for any reason the administration of an inhalation anesthetic is undesirable, the patient can be rendered unconscious by the

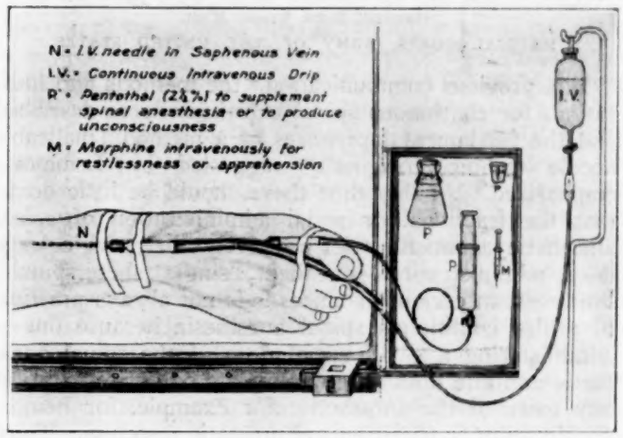
N = I.V. needle in Saphenous Vein
I.V. = Continuous Intravenous Drip
P = Pentothal (2½%) to supplement spinal anesthesia or to produce unconsciousness
M = Morphine intravenously for restlessness or apprehension
I.V.
N
P
M

Fig. 13.—Details of intravenous drip and supplementary intravenous agents.

use of an intravenous barbiturate such as pentothal sodium. The placing of an intravenous needle in one of the great saphenous veins near the medial malleolus and maintaining a slow drip of fluid through the needle throughout the entire operative procedure permits the rapid administration of supportive fluids such as glucose, blood and plasma or the administration of an intravenous anesthetic agent (fig. 12).

With the use of a technic which distributes the major portion of the anesthetic solution in the spinal canal at the level from which the nerves supplying the upper part of the abdomen arise, the need for supplementary anesthesia because of insufficient duration becomes less frequent. However, if it becomes obvious that the operation is going to outlast the anesthesia, a supplementary anesthetic must be employed. Pentothal sodium is an excellent intermediary agent facilitating the transition from spinal to inhalation anesthesia. This transition can usually be made without any disturbance of the operative field, provided the supplementary agents are started before the patient begins to feel pain or there is any loss of muscular relaxation.

With the increasing use of continuous spinal anesthesia,[3] the need for supplementary anesthesia for longer surgical procedures is disappearing. This technic is valuable and has made spinal anesthesia practical for a large group of patients for whom it was frequently unsatisfactory or inadequate.

With the use of proper agents and methods and with an appreciation of some of the physical and physiologic factors involved in the production of adequate spinal anesthesia, the distribution of the agent in the spinal canal can be fairly accurately controlled. If this control of the anesthesia is combined with the judicious use of supportive measures and supplementary agents, there are few patients to whom spinal anesthesia need be denied for surgery in any part of the abdomen.

The prime contraindication to spinal anesthesia is still the absence of a spinal anesthetist.

2. Melville, K. I.: Combined Ephedrine-Pituitary Extract (Posterior Lobe) Therapy in Histamine Shock, J. Pharmacol. & Exper. Therap. **44**: 279-293 (March) 1932. Raginsky, B. B.: The Present Status of Analeptics in Anesthesia, Tr. Am. Coll. Surgeons **1**: 66-73 (July) 1938.

3. Schuhmacher, L. F., Jr., and Eversole, U. H.: Technics of Spinal Anesthesia, Anesthesiology **3**: 630-643 (Nov.) 1942. Lemmon, W. T.: A Method for Continuous Spinal Anesthesia, Ann. Surg. **111**: 141-145 (Jan.) 1940

# THE USE OF CONTINUOUS SPINAL ANESTHESIA

## UTILIZING THE URETERAL CATHETER TECHNIC

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MEDICAL CORPS, ARMY OF THE UNITED STATES

In a previous communication [1] the methods and indications for continuous spinal anesthesia were described and the fundamental premises of a method (malleable needle technic) originally suggested by Lemmon [2] emphasized. At this time there should be little doubt that the fractional or serial administration of spinal anesthetic agents is safer relatively than single large dose administration—so-called "single shot spinal." However, in certain instances it is not always practical to utilize continuous spinal anesthesia because one is administering a small initial dose of the spinal anesthetic and one does not contemplate or desire to inject any more of the anesthetic; for example, for hemorrhoidectomy or transurethral prostatic resection. Thus, certain surgical procedures do not lend themselves as practical for utilizing continuous spinal anesthesia regardless of the technic employed.

The continuous spinal method is indicated usually and advantageously in such surgical operations as bilateral primary inguinal herniorrhaphy, operations for recurrent hernias (inguinal or ventral), certain abdominal laparotomies in which the surgical risk is good, such as operations on the biliary tract or stomach, lengthy orthopedic procedures on the hips or lower extremities and neurorrhaphies of the sciatic nerve. At this juncture it should be stated again that debility and cachexia and impending surgical shock should deter one from the use of a spinal anesthesia by any method. I believe that there are few if any exceptions in these situations.

The chief difficulties which I have experienced coincidental with the Lemmon technic [2] have resulted from the dislodging of the malleable needle from the subarachnoid space, thus invalidating the effectiveness of the procedure. It is true that on occasion it has been difficult to introduce the malleable needle satisfactorily into the subarachnoid space, but this objection is relatively negligible. Breakage of the needle is a remote but actual hazard to be conjured with continually. In an effort to obviate the difficulty of the malleable needle becoming displaced, a new method of performing continuous spinal anesthesia was devised utilizing a ureteral catheter. Previous reports of the use of a ureteral catheter for caudal anesthesia [3] and for continuous subarachnoid drainage for meningitis as advocated by Love [4] prompted the trial of a ureteral catheter for the purpose of continuous spinal anesthesia. It was my feeling that a number 4 ureteral catheter would be less traumatic to tissues than a needle (malleable) when it is left in position for the duration of an operation, and if the catheter was satisfactorily introduced into the subarachnoid space it would not become dislodged as easily as a needle. The hazard of breakage of the catheter during any portion of the procedure did not appear to be as great as that with a needle, because of the flexibility and mobility of the catheter; nevertheless this complication is potentially a possibility.

Read before the Section on Anesthesiology at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 14, 1944.

1. Tuohy, E. B.: Continuous Spinal Anesthesia: Its Usefulness and Technic Involved, Anesthesiology **5**: 142-148 (March) 1944.
2. Lemmon, W. T.: A Method for Continuous Spinal Anesthesia, Ann. Surg. **3**: 141-144 (Jan.) 1940.
3. Adams, R. C.; Lundy, J. S., and Seldon, T. H.: Continuous Caudal Anesthesia or Analgesia: A Consideration of the Technic, Various Uses and Some Possible Dangers, J. A. M. A. **122**: 152-158 (May 15) 1943. Manalan, S. A.: Caudal Block Anesthesia in Obstetrics, J. Indiana M. A. **35**: 564-565 (Oct.) 1942.
4. Love, J. G.: Continuous Subarachnoid Drainage for Meningitis by Means of a Ureteral Catheter, J. A. M. A. **104**: 1595-1597 (May 4) 1935.

### TECHNIC

The introduction of the ureteral catheter (x-ray type, leaded with a round tip) number 4 is accomplished by the following method: The patient is placed on the table in the lateral recumbent position, usually on the patient's right side, shoulders and hips perpendicular to the table and close to the edge, the thighs flexed on the abdomen so that the patient's knees and chin are close together. The skin is surgically prepared and sterile drapes are placed about the site of the injection. The space between the third and fourth or fourth and fifth lumbar vertebrae is used for the site of injection. Occasionally the space between the second and third lumbar vertebrae is utilized if the lower lumbar interspaces appear to be rather narrow. The skin and subcutaneous tissues at the site of the injection are anesthetized then with 1 per cent solution of procaine hydrochloride. In most instances 25 to 50 mg. of ephedrine sulfate is injected intramuscularly at the site of injection prior to the administration of the spinal anesthetic. In order to facilitate the introduction of the 15 gage needle which is to guide the ureteral catheter, the skin at the site of the puncture is broken by means of a skin awl. Following this the 15 gage needle, 3 to 3½ inches (7 to 9 cm.) in length, with a flush fitting stylet, is inserted into the subarachnoid space. A definite "snap" is felt when the needle penetrates the ligamentum flavum and thence the dura and arachnoid tissue. On completion of a successful puncture of the arachnoid the stylet is removed and a 20 cc. luer syringe containing 400 mg. of procaine or metycaine hydrochloride (4 cc. of a 10 per cent solution) is attached to the hub of the needle and the anesthetic agent is diluted with spinal fluid up to a total volume of 12 to 15 cc. The resultant mixture is a 3⅓ or 2⅔ per cent solution. The concentration of the solution can be varied at will by altering the amount of spinal fluid withdrawn. Solutions of less than 2 per cent or over 4 per cent concentration seldom are necessary. The more dilute solutions, for example, 2 to 2.5 per cent, are used usually for operations in the upper part of the abdomen because they will allow the injection of a greater volume of solution without increasing the initial total dose, and thus segmental dermatome anesthesia will be produced sufficiently high. The syringe is removed from the needle hub and the ureteral catheter is inserted through the needle into the subarachnoid space. Centimeter markings on the catheter are used to measure with so that one can determine how far to introduce the catheter. The tip of the catheter is advanced about 4 to 5 cm. beyond the end of the point of the needle into the subarachnoid space. This is sufficiently far to prevent the catheter from slipping out of place. The 15 gage needle is removed from the intervertebral space and slid off the free end of the catheter. A 22 gage needle ½ inch (1.27 cm.) in length is inserted into the free end of the catheter and to this needle hub is attached a one way stopcock adaptor. One end of this adaptor fits the hub of the 22 gage needle and the other the syringe containing the

anesthetic solution. Originally I did not use a one way adaptor, but without it I have had several cases in which the spinal fluid pressure was sufficient to force the plunger back into the syringe and consequently alter the concentration of the solution; so I have added the one way adaptor and obviated this difficulty. Preparations for injecting the spinal anesthetic via the catheter now are complete. As the bore of the number 4 ureteral catheter is so small, little solution is needed to fill its lumen, and it is not necessary to allow for the minute loss of solution in calculating dosage of the anesthetic agent. Initial doses will vary between 80 and 120 mg. In general the original fractional dose should be a fourth or fifth less than the dose contemplated for a single injection type of anesthesia.

When the initial dose has been injected the patient is turned carefully onto his back and the catheter is brought out to his side and fastened in place to the operative mattress with adhesive plaster. Additional quantities of the anesthetic agent should be injected at the first indication that the patient is having pain or that there is a lack of muscular relaxation. Usually within thirty-five to forty minutes it is necessary to add additional amounts (2 cc., or 52-66 mg.) of the anesthetic agent. Subsequent doses are added in the same manner as they are required.

At the completion of the operation, before an attempt is made to remove the catheter, the patient is turned on his side again and if possible the thighs and head are flexed and then the catheter is withdrawn gently from the subarachnoid space. The purpose of flexing the patient is to relieve any tendency for the interspinous ligaments and spinous processes of the vertebrae to impinge on the catheter.

### COMPLICATIONS

There has been no increase in the incidence of spinal puncture headache as compared with single dose spinal anesthesia or routine spinal puncture. There have been no instances of persistent paresthesia in the limited number of cases so far (250). Bleeding from the soft tissues at the site of injection is encountered occasionally, but only if difficulty has been experienced in making the lumbar puncture. Failure to introduce the catheter successfully has occurred in 2 cases. No instances of bladder or rectal dysfunction have been noted. There has been no evidence so far of any infection in the subarachnoid space or in the soft tissue.

### COMMENT

At present the catheter technic, as compared with the use of the malleable needle, has been attended by fewer mechanical difficulties in my experience. There have been no situations in which the catheter has inadvertently slipped out of the subarachnoid space. It has been my opinion that the catheter causes less trauma to the soft tissues than does a needle over a protracted period of time.

The failure to insert the ureteral catheter easily in some cases has been found to be due to the fact that the 15 gage needle was advanced too far intrathecally and insufficient space was remaining between the point of the needle and the body of the vertebrae to allow the catheter to pass. If the needle is withdrawn slightly, with an effort meanwhile to advance the catheter, entrance of the catheter into the subarachnoid space will be accomplished. One precaution must be exercised; namely, that the catheter should not be withdrawn through the needle once the catheter has entered the subarachnoid space, because the sharp point and bevel of the needle may shear off the catheter. If the catheter must be removed or partially withdrawn for any reason during the procedure. the needle should be withdrawn first from the lumbar interspace. The direction (cephalad or caudad) which the catheter will advance in the subarachnoid space after the tip of the catheter leaves the end of the guiding needle cannot be predicted positively; however, if the round tip of the catheter is bent slightly before it is introduced into the lumen of the needle, I have found that the catheter will advance cephalad in most cases. This has been verified radiographically by using the leaded ureteral catheters. In the event that the catheter turns caudad on entering the subarachnoid space, this fact can usually be detected shortly after the initial dose of the spinal anesthetic has been introduced because of the segmental distribution of the resulting anesthesia. When this situation occurs it is suggested that the remaining amount of the anesthetic solution in the syringe be diluted with an equal volume of isotonic solution of sodium chloride, and twice as much solution (volume) should be administered in order to produce higher dermatome anesthesia. Barbotage is not recommended, but it can be accomplished via the catheter if it is deemed necessary.

This procedure (ureteral catheter technic) has been taught to student officers in training in anesthesiology and I think the technic cannot be too difficult, as they can successfully use the equipment without perceptible difficulty in a relatively short time. I know that some other anesthetists are using this method, and it appears to be satisfactory also in their experience. The challenge that the 15 gage needle is unnecessarily traumatic for subarachnoid puncture is accepted, but in retaliation I offer the data that up to the present time no untoward effects have resulted from the use of this 15 gage needle, and it has been just as easy to insert this needle as it has been the malleable needle used with the Lemmon procedure. It has appeared to me that the efficient operation of the catheter system is an improvement in achieving the fundamental principles of continuous spinal anesthesia as originally suggested by Lemmon. Naturally it will be necessary to have further experience with a larger series of cases to have a complete evaluation of this method, but I think that it is worthy of trial and is to be recommended as an adjunct to this type of anesthesia. The total cost of this equipment is relatively small as compared with the equipment necessary with other methods of continuous spinal anesthesia. This may or may not be an important factor.

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## ABSTRACT OF DISCUSSION

### ON PAPERS OF DRS. EVERSOLE AND TUOHY

DR. WILLIAM T. LEMMON, Philadelphia: With an experience of over 15,000 cases and with the record of low mortality, it is hard to have much to say except in complement of the work done by Dr. Eversole. He hit the keynote when he said it is not the drug, it is not the method, but the trained man who is giving the anesthesia. I would rather have a trained anesthetist anesthetize me or my patients than to have a much superior method with an absence of training and experience. When this method is used by others of lesser training and experience it produces death—rapid, sudden and dramatic death. I know that, because I was selected to be on the Anesthesia Study Commission of the Philadelphia County Society with

Dr. Ruth, and we have the cases and the records. The trouble is not with the method, it is not with the drug, but it is either with the patient or with the individual handling the method and administering the drug. Every method that was instituted to help the patient was always instituted too late, and the means of getting out of difficulties were usually injection of epinephrine into the heart, which from our experience should never be used, because every one of those patients died. I know in the hospitals around Philadelphia County that we have the anesthetists on the alert. They know that if anything happens we are going to have not only a hospital investigation but a study of that case, and we want to find out where the fault is. The contraindications to spinal anesthesia are practically nil, but the contraindications to surgery plus spinal anesthesia are many. You cannot improperly prepare a patient for surgery and expect him to take surgery and anesthesia. If a patient is prepared for surgery he will take the handicap of the anesthesia in his stride, so to speak. Anything that is a contraindication must be eliminated before the doctor operates on his patient. I want to compliment Major Tuohy on his ingenious idea and method of using the ureteral catheter in the production of continuous spinal anesthesia, because if its disadvantages are outweighed he has a definite advantage in that his catheter will not become displaced. That, in the hands of the inexperienced, is one of the big troubles.

DR. URBAN H. EVERSOLE, Boston: Dr. Lemmon stressed an important point when he spoke of the dangers of this technic. I assume he meant the dangers of this particular technic in contradistinction to the inherent dangers of all types of spinal anesthesia. I accept that criticism. In my opinion, in the virtue of the technic lies its danger. There is a wide margin between the specific gravity of the solution injected and the specific gravity of spinal fluid. This enables the anesthetic agent to run cephalad rapidly. With this rapid cephalad progression there is the danger that it will go too high, and respiratory paralysis will ensue. As to the question concerning the administration of dextrose into the spinal canal, I am sure that 10 per cent dextrose can be satisfactorily sterilized without chemical change. I do not hesitate to put sterilized 10 per cent dextrose into the spinal canal after having done it in nearly 20,000 cases.

MAJOR E. B. TUOHY, M. C., A. U. S.: With regard to the question which Dr. Romberger brought up concerning the sterilization of the catheters, I agree full well with him, and I feel more safe myself if the catheters are autoclaved under high pressure. This is by far the best technic. However, the catheters do not stand the sterilization quite as well by this means. The lacquer which is on the outside of the catheters will break down a little more rapidly on protracted and repeated sterilization. In my experience so far I have been able to use the catheters for ten or twelve separate cases. This implies, of course, that there is careful scrutiny of the continuity of the catheters and the way in which they are handled. Concerning the indications of whether or not spinal anesthesia will be used for the type of cases which Dr. Romberger mentioned, I have no bone to pick on that score. One has to be a little cautious in what is written in the literature with regard to spinal anesthesia when you say that this method may be used for such and such a type of case. I have had no experience in the use of epinephrine or similar vasoconstrictor substances in conjunction with the subarachnoid injection of anesthetic agents.

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**Hospital Facilities in Japan.**—Hospital facilities in Japan are not sufficient to meet the needs of the people (19 beds per 10,000 people, as compared to the average for the entire United States of 97 beds per 10,000 people). . . . The greatest number of hospital beds (about three fifths) is found in the larger cities, whereas the rural areas have only small dispensaries. The larger hospitals, connected with the medical schools, compare favorably both in reputation and in equipment with teaching hospitals in Europe; but in the smaller cities and towns hospitals are little more than rest homes.—Simmons, James S., and others: Global Epidemiology, Philadelphia, J. P. Lippincott Company, 1944.

# INTERNSHIPS AND RESIDENCY TYPE TRAINING IN UNITED STATES NAVAL HOSPITALS

VICE ADMIRAL ROSS T. McINTIRE (MC)
Surgeon General, United States Navy
WASHINGTON, D. C.

The Medical Corps of the Navy has been interested for a long time in the development and fullest possible utilization of the notable facilities it possesses for graduate educational training of its medical officers. The United States Naval Hospitals on this continent are as fine as any hospitals in the world; many of the United States Naval Dispensaries are actually small hospitals staffed, equipped and conducted along lines comparable to the best of civilian hospitals of similar size; and some of our fleet hospitals and others in outlying areas even near to combat zones are so conducted that all of these activities and facilities provide outstanding training opportunities for young doctors.

This interest in the development of an educational program was not solely for the benefit of the medical officers assigned to these activities but primarily and fundamentally because we are concerned with everything which counts for improvement and betterment in standards of medical care of our patients. It has been entirely incidental, therefore, that better than average opportunities for internship and residency type training are thus provided for our medical officers. As a morale builder nothing could be more important than that these men may receive substantial training while on active duty, thus increasing their medical stature and affording them opportunities to make better doctors of themselves.

## INTERNSHIPS

General rotating internships in naval hospitals were established in 1924. At the present time thirty-eight naval hospitals have been approved by the Council on Medical Education and Hospitals of the American Medical Association for internship training on the same standards as those of civilian hospitals.

Under the accelerated program these naval internships consist of a nine months rotating service, providing all interns with three months on each of the three groups of services according to the following general schedule:

1. Medicine, neuropsychiatry and clinical laboratory.
2. Surgery, urology, ophthalmology, otolaryngology and roentgenology.
3. Obstetrics, pediatrics and gynecology.

These internships are acceptable for credit before state boards of licensure to the same extent as similar internships in civilian hospitals.

In order to maintain approved standards for internships certain essentials are necessary. Following a recent review of the internship training program in naval hospitals by the Board of Honorary Consultants to the Surgeon General of the Navy, the general standards governing internship training in naval hospitals are those outlined by the Council on Medical Education and Hospitals of the American Medical Association [1] for civilian institutions as adapted to naval needs.

1. Essentials of an Approved Internship, J. A. M. A. **118**: 1497 (April 25) 1942.

RESIDENCY TYPE GRADUATE TRAINING

United States Naval Hospitals in general are organized and staffed along departmental lines in the specialties with standards of practice in these institutions so complete and so competently conducted that the training received by naval medical officers assigned to duty in these activities has long been recognized as the equal of any formal residency in the better teaching and other civilian hospitals. However, these activities had never sought to be formally surveyed and listed as providing residency training according to civilian standards by such organizations as the Council on Medical Education and Hospitals of the American Medical Association and the American College of Surgeons until the middle of last year, when it was determined that such formal recognition would be advantageous to all concerned. One of the important functions undertaken by the newly established Professional Division of the Bureau of Medicine and Surgery of the Navy Department immediately on its inception in 1944 was that of a formal graduate educational program. This included a review of these opportunities for graduate training in medicine and its specialties, and the making certain that all of our naval hospitals would have adequate libraries, staff and departmental conferences, bedside instruction and other essentials to such training along conventional lines.

From the beginning of mobilization many noted medical teachers and specialists had come into service as reserve officers; many younger men in the midst of their residencies in various of the specialties left these to be commissioned in the Navy; many of our regular naval medical officers had been given special courses of varying lengths; and we still have innumerable young medical officers coming to us direct from civilian hospital internships or even fresh from medical schools to intern in our naval hospitals. Consequently we have had the necessary elements for outstanding teaching and instruction with younger men whose careers were otherwise being interrupted and still younger recently graduated officers, eager for opportunities to train and develop themselves. Not all of the latter want to be specialists, nor do we want them to be, but we do wish to make of them the best possible type of doctors primarily and fundamentally, as mentioned before, for the benefit of our sick and wounded, and incidentally for their own benefit.

Any straight service in a single department or through a group of allied specialties, following one year of rotating internship, is classed as a residency. The Council, the American boards certifying in the specialties, the American College of Physicians and the American College of Surgeons are concerned with this subject of residency type graduate training. The Council and the American boards, acting jointly, review and survey facilities for this work in all the specialties; the American College of Surgeons similarly surveys for formal approval of residencies in surgery and the surgical specialties. Lists are published annually by the American Medical Association and the American College of Surgeons carrying the names and locations of hospitals, civilian and others, granted such official approval and recognition. Certain essentials of graduate education in the specialties are required to obtain such approval and listing and these are outlined in detail by both of these organizations.[2] Outstanding among these requirements are adequate library facilities and staff conferences, as well as bedside clinical instruction.

Lists of current periodicals and books considered minimum for an acceptable library are supplied each naval hospital through the Bureau of Medicine and Surgery based on the recommendations of the aforementioned organizations concerned with graduate medical education. The minimum requirements for a good library are thus established by this bureau, and this minimum will be found uniform in all naval hospitals. It is obvious that these libraries will be further augmented by certain additional journals and many other books, especially in hospitals designated for the care of certain special types of diseases or illnesses. Nursing and dental publications are included.

It is directed also that staff conferences include, as a minimum, one departmental staff meeting weekly (interdepartmental conferences may be arranged between related departments) and a general staff meeting at least twice monthly. Clinicopathologic conferences and literature reviews ("Journal Club meetings") at regular intervals may be incorporated as part of either program. In larger activities the latter conferences are preferable in the departmental meetings, while in the smaller activities they may become part of the regular general staff conferences or may be separate from them but including all departments as an additional general conference.

All activities providing residency type training in the specialties must make annual reports in triplicate to the Bureau of Medicine and Surgery of the Navy covering periods of assignment of junior medical officers to such services, so that credit for the time spent may be recorded in the biographic files of (*a*) the American Medical Association, (*b*) the American College of Surgeons (in the surgical specialties) and (*c*) the Bureau of Medicine and Surgery.

Junior medical officers assigned to specialty services in naval hospitals will not be termed residents, nor will such services be designated formally as residencies. However, periods of service in activities approved officially for residency type training are given credit before the American boards and others. Services in unapproved activities are recorded as unclassified, but the officer may be able in many such instances to obtain official American board or other recognition for time spent in assignment to such services. Cumulative credit is obtainable for interrupted periods of service during wartime. Less than six months in any service will usually require individual consideration for credit.

Officers asking credit for eventual certification by one of the American boards have been advised to write to the secretary of the board concerned requesting a copy of the "Record of Professional Assignments" which is kept by him as a log of his activities. The latter are attested by his commanding officers for later use whether his service assignments in a given specialty have all been in officially approved activities or in facilities such as naval dispensaries not so listed but nevertheless providing outstanding experience under qualified supervision.

For the present, only naval hospitals have been directed by this bureau to make formal application for official approval of residency type training. Medical officers in command of other smaller naval facilities where opportunities exist for outstanding graduate training in any of the specialties may make arrangements for similar application through the bureau whenever in the opinion of the commanding officer this is

2. Essentials of Approved Residencies and Fellowships, J. A. M. A. **113:** 794 (Aug. 26) 1939. Minimum Standard for Graduate Training in Surgery, Bull. Am. Coll. Surgeons **29:** 432 (Dec.) 1944.

justified. Medical officers serving in naval dispensaries, hospitalizing certain of their patients in affiliated civilian institutions, such as in departments of obstetrics and gynecology, otolaryngology or pediatrics, will receive official board and other credit if these affiliated hospitals are already approved by the Council and the colleges.

### WARTIME AND PEACETIME OPPORTUNITIES FOR GRADUATE TRAINING

It is clearly recognized and frankly stated that many naval officers will have little or no opportunity for such training during wartime because of the tremendous pressure and need for medical officers on our ships and in our outlying stations. It is a fact, nevertheless, that many others do have such opportunities while actually performing their military duty if fortunate enough to obtain such assignments as these that have been described. Several notable policies have been consistently followed, as far as this was possible under the circumstances of wartime stress.

A constant effort has been made by the Personnel Division of the Bureau of Medicine and Surgery to assign men with outstanding training in a specialty to service in that specialty where he is obviously most proficient. This policy extends downward through the ranks of those with lesser degrees of proficiency or only partial training.

All naval officers, except those classified for limited duty, are expected to have a period of sea duty fairly soon after their induction into service. On nearing the completion of this they are encouraged to express preference for future assignments nearer home. It is logical that these assignments should be consistent so far as possible with the previous experience and proficiency of the man concerned.

It is true that the assignment of an officer already partially trained in a civilian residency may have to be changed before his full training, according to American board or college requirements, can be completed by us. Credit for this time spent will nevertheless be his and in the meantime that naval hospital will have had the advantage of the partial training this young man had had. He may need to be sent out to some other type of duty, or it may become necessary to assign him to another naval hospital, but in the latter event time will accumulate to his credit. We cannot promise anything in advance about services these days, but to the extent that has been outlined these plans are logical, consistent, and to a large degree workable.

What this program of graduate educational training in naval hospitals will mean to the rehabilitation of medical officers before return to civilian practice, and what it will mean for the future of the regular naval Medical Corps, can be only incompletely estimated. One thing is certain: the establishment of such programs in our institutions will unquestionably be maintained into peacetime. Regular Navy officers of the Medical Corps now and in the future have opportunities for specialization and achievements in the medical profession quite comparable to those of civilian life, whereas heretofore such opportunities have been either limited or not fully promoted. Certification by the American boards, far greater participation in the activities of the colleges and other national organizations and recognition of attainments should follow in the future for officers of the regular Medical Corps along the same lines as those that are so common to the civilian medical profession.

Finally, let it be reemphasized that there is no greater stimulus to good medical care of patients than to incorporate a program of graduate medical education for the officers serving and caring for these patients. This truism applies to all medical officers of any hospital from the top down.

Better study of the patients, careful supervision and personal clinical instruction of younger medical officers by older teachers, departmental and staff conferences for discussion and constructive criticism, the constant use of good libraries, and other similar advancements, even now while we are in the midst of war are both possible and necessary for the basic purpose of maintaining and improving the standards of medical care given the sick in our hospitals. The educational aspects of all this are incidental, it is true, but they are there and the opportunities afforded by them are magnificent.

It will be clear from the foregoing that we intend our good records for medical care of patients in the past shall be not merely maintained but steadily improved. We have the not unwarranted feeling that Navy trained physicians will be well to the front among the leaders of the profession in the future when peace comes again.

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## BORIC ACID OINTMENT

### A STUDY OF POSSIBLE INTOXICATION IN THE TREATMENT OF BURNS

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Boric acid ointment has been used for many years as an antiseptic and bland preparation for the treatment of burns. The favorable results obtained in treatment of the victims of the Cocoanut Grove disaster when boric acid ointment or white petrolatum was used under pressure dressings resulted in an official recommendation of this type of therapy by the Subcommittee on Burns of the National Research Council.[1] On the basis of these findings a circular letter was sent by the Bureau of Medicine and Surgery to all medical officers in which this form of treatment was summarized. At that time Cope [2] suggested that "too rapid absorption of boric acid might result in poisoning." Analyses of the urine of 20 of his patients showed that a maximum of 2.0 Gm. of boric acid might be excreted in the first twenty-four hours by patients with extensive burns. Later when saturated boric acid solution was used to irrigate granulating wounds as much as 2.5 Gm. was excreted in the urine in twenty-four hours. All patients maintained

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Dr. A. C. Ivy suggested the problem to the authors. Dr. William M. Mann of the National Zoological Park supplied the bear. Lieut. W. V. Consolazio, H-V(S), U.S.N.R., made the blood electrolyte analyses. Ensign O. E. McElroy, W-V(S) (H), U.S.N.R., and Dr. H. F. Blum made the spectrographic analyses. Technical assistance was given by H. Holland, PhM1c, V-10, U.S.N.R., E. Jenny, PhM1c, V-10, U.S.N.R., V. Latta, PhM2c, V-10, U.S.N.R., and E. Hornby, PhM2c, V-10, U.S.N.R.

1. New Recommendations on Treatment of Burns and Wound Infections, Medicine and the War, J. A. M. A. **122:** 813-814 (July 17) 1943.

2. Cope, Oliver: Care of Victims of the Cocoanut Grove Fire at the Massachusetts General Hospital, New England J. Med. **229:** 138-147 (July 22) 1943; The Treatment of the Surface Burn, Ann. Surg. **117:** 885-893 (June) 1943.

normal kidney function, and these investigators concluded that prompt excretion did not lead to toxic levels of boric acid in the body.

In May 1943 Dr. A. C. Ivy suggested that in view of this recommendation further studies should be made on the toxicity of boric acid, with particular attention to the effect on bone marrow since severe anemia was one of the constant late findings in extensively burned patients. The immediate need of this study, however, was decreased by the recommendation of a joint session of the Subcommittees on Burns and Surgical Infections on July 17, 1943, in which it was recommended that boric acid ointment be discontinued in the treatment of burns. Since this official ointment has been widely used and will continue to be used by others [3] and since the studies could be prosecuted at a reduced rate along with our more urgent naval medical problems, the question of possible boric acid toxicity has been slowly but exhaustively studied at a relatively low priority level.

## HISTORICAL

The literature on boron poisoning may be divided into two categories: instances of poisoning presumably due to absorption of boric acid from wounds and burns, and cases of poisoning due to oral ingestion of boron.

In 1905 Dopfer [4] first noted an intoxication which he ascribed to the application of 10 per cent boric acid ointment to a burn measuring 12 by 3 cm. in the axillary region of a 2 year old child. Eighty Gm. of ointment was applied over a period of four days. When seen by the physician on the fourth day the wound was granulating and not infected. The most evident sign of intoxication was a red rash, which had developed on the back and elbows on the second day and spread over the whole body. The patient was moribund and died in thirty minutes. Pathologic changes were not evident at autopsy. Savariaud [5] in 1914 suggested that, while boric acid solution might be harmless, wounds should never be dusted with powdered boric acid since he had seen serious intoxication develop in twelve hours in an 8 year old child whose burns of the abdomen and thighs were dusted with boric acid. Gissel [6] in 1933 reported probable poisoning of a 4 year old child whose severe burns were treated with 30 Gm. of powdered boric acid. The symptoms noted were fever, "weakening of the circulation," diarrhea, vomiting, conjunctivitis, stupor and terminal bronchopneumonia. At autopsy, four days later, lesions other than the pneumonia and degeneration of the liver and kidneys were not found. Brose [7] in 1883 reported a death following the use of powdered boric acid on a chronic leg ulcer. Best [8] in 1903 noted a similar death of an adult male when 6 ounces (170 Gm.) of powdered boric acid was used in a wound following excision of some inguinal lymph nodes. While these cases leave much to be desired as proof of boron intoxication is concerned, other cases in the literature in which the boron was given by routes in which absorption is certain leave no doubt that serious or even fatal boron intoxication can occur.

Poisoning by enemas of boric acid has been described by Sanders,[9] by Bazin,[10] by Brown and his associates,[11] after accidental injection by Peyton and Green,[12] who had a patient recover after a single subcutaneous dose of 28 Gm., and by McIntyre and Burke,[13] who had a patient recover after 15 Gm. of boric acid had been given intravenously. Owing presumably to the almost complete absorption of boric acid from solutions, by far the most insidious form of intoxication is that which occurs on irrigation of a closed cavity with saturated boric acid solution. Molodenkow, quoted by Tillmanns,[14] and more recently Ross and Conway [15] have reported deaths due to absorption of boric acid from irrigated cavities.

Numerous cases of poisoning from the accidental oral ingestion or oral therapeutic use of boric acid or borax as preservatives have been reported.[16] Poisoning has also been described in infants who have suckled from nipples cleansed with saturated boric acid solution.[17]

From the numerous case histories reported, it appears that the fatal dose of boric acid in an adult is somewhat more than 15 to 20 Gm., in an infant 5 to 6 Gm.[18] The symptoms which may be encountered in poisoning are depression of the circulation, persistent vomiting and diarrhea, followed by profound shock and coma. The temperature is usually subnormal, and most observers describe a scarlatinaform rash, which may cover the entire body. If recovery occurs, the areas affected by the rash usually desquamate and this process may extend to the mucous membranes. The clinical course may take three to five days, and death has occurred frequently four to five days after the source of poisoning was removed.

Only two groups of workers provided proof that the intoxication was due to boric acid by showing on chemical analysis that the patients had relatively large amounts of boric acid in all tissues. McNally [18] was the first to show that the highest level of boric acid occurred in the brain and the liver. Of the 6 infants whose tissues were analyzed they found an average level of 210 mg. per hundred cubic centimeters in the brain and 182 mg. per hundred cubic centimeters in the liver. These infants were accidentally fed 60 to 150 cc. of a saturated boric acid solution and died two days later. Ross and Conway [15] give an excellent account of intoxication in a 3 year old child who had continuous irrigation of the left pleural space with 5 per cent boric acid solution for empyema. Four liters per day for three days was used for this irrigation, at the end of which time the patient was in profound shock and the neck,

3. McClure, R. D., and Lam, C. R.: A Statistical Study of Minor Industrial Burns, J. A. M. A. **122:** 909 (July 31) 1943. Clowes, G. H.; Lund, C. C.; and Levenson, S. M.: Surface Treatment of Burns, Ann. Surg. **118:** 761-779 (Nov.) 1943.

4. Dopfer: On a Fatal Accident Following the Use of Official 10 per Cent Boric Acid Ointment in a Burn, München. med. Wchnschr. **52:** 763, 1905.

5. Savariaud, in Serious Poisoning by Boric Acid Dressing, Paris Letter, J. A. M. A. **63:** 593 (Aug. 15) 1914.

6. Gissel, H.: Toxicity of Boric Acid, Quart. J. Pharm. & Pharmacol. **6:** 714, 1933.

7. Brose, L. D.: Death Following the External Use of Powdered Boric Acid, M. News, Philadelphia **43:** 199, 1883.

8. Best, C. L.: Boric Acid Poisoning: Report of a Fatal Case with Autopsy, Tr. Chicago Path. Soc. **6:** 161-168, 1903-1904.

9. Sanders, J. H.: Boracic Acid Poisoning, Brit. M. J. **1:** 605-606 (March 16) 1912.

10. Bazin, A. T.: Acute Boracic Acid Poisoning, Canad. M. A. J. **14:** 419-420 (May) 1924.

11. Brown, W. L.; Brown, C. P., and Murphy, J. L.: Toxicity of Boric Acid, J. A. M. A. **106:** 1221 (April 4) 1936.

12. Peyton, H. A., and Green, D.: Boric Acid Poisoning: Case Report, South. M. J. **34:** 1286-1288 (Dec.) 1941.

13. McIntyre, A. R., and Burke, J. C.: Intravenous Boric Acid Poisoning in Man, J. Pharmacol. & Exper. Therap. **60:** 112-113 (June) 1937.

14. Molodenkow, quoted in Tillmanns, H.: Textbook of Surgery, translated by B. T. Tilton, ed. 2, New York, D. Appleton & Co., 1899, vol. 1, p. 160.

15. Ross, C. A., and Conway, J. F.: The Dangers of Boric Acid, Am. J. Surg. **60:** 386-395 (June) 1943.

16. McWalter, J. C.: Note on the Effects of Borax on Infants, Lancet **2:** 369 (Aug. 10) 1907. Willson, P.: A Case of Boric Acid Poisoning, Washington M. Ann. **14:** 329-331, 1915. Forsythe, D.: Celiac Disease or Boric Acid Poisoning, Lancet **2:** 728-730 (Oct. 25) 1919. Potter, Caryl: A Case of Borax Poisoning, J. A. M. A. **76:** 378 (Feb. 4) 1921. Birch, John: Fatal Poisoning by Borax, Brit. M. J. **1:** 177 (Feb. 4) 1928. Buzzo, A., and Carratala, R. D.: The Toxicity of Boric Acid and of Borates Used as Preservatives and Antiseptics, Rev. Asoc. méd. argent. **46:** 1493-1495 (Nov.) 1932. McNally and Rust.[18]

17. Aikman, John: Strychnine Poisoning in Children, J. A. M. A. **95:** 1661-1665 (Nov. 29) 1930.

18. McNally, W. D., and Rust, C. A.: The Distribution of Boric Acid in Human Organs in Six Deaths Due to Boric Acid Poisoning, J. A. M. A. **90:** 382-383 (Feb. 4) 1928.

thorax and extremities were covered with an erythematous rash. Death occurred twenty-four hours after the irrigation had been stopped. Chemical analyses revealed 112 mg. per hundred cubic centimeters in the brain and 13.7 mg. per hundred cubic centimeters in the liver. These authors made a comprehensive summary of the literature and suggest that boric acid is much more dangerous than is generally assumed.

TABLE 1.—*Acute Toxicity of Boric Acid in Various Species By Different Routes of Administration*

| Animals | Route | L. D. 50, Mg. per Kg. | Slope | Standard Error, Mg. |
|---|---|---|---|---|
| 60 mice | Subcutaneous | 2,070 | 4.7 | ± 150 |
| 40 mice * | Subcutaneous | 1,740 | 8.0 | ± 130 |
| 40 mice | Intravenous | 1,780 | 8.9 | ± 121 |
| 30 mice | Oral | 3,450 | 14.0 | ± 158 |
| 40 rats | Intravenous | 1,330 | 6.3 | ± 112 |
| 45 rats | Oral | 2,660 | 7.7 | ± 220 |
| 45 guinea pigs | Subcutaneous | 1,200 | 7.3 | ± 80 |

* Solution adjusted to $p_H$ 7.4 with sodium hydroxide.

Since the very early (1904) studies by Wiley [19] on borax and boric acid as food preservatives but little additional pharmacologic work has been done to evaluate boric acid as a toxic agent. The unusual distribution of boron in the body, where, in contrast to other poisons, most is found in the brain, should have stimulated additional studies. Certainly, greater knowledge regarding the acute and chronic toxicity of boric acid, including its absorption from wounds, excretion and studies on histopathology, are needed before its possible toxic effect can be properly evaluated.

## METHODS

*Boric Acid.*—Boric acid was determined on aliquot samples of tissue or urine after ashing by direct titration in the presence of glycerol.[20] In a series of 32 urines to which were added varying known amounts of boric acid, the mean recovery on analysis was 89 per cent. Spectrographic analysis for the boron lines in brain and liver fractions was done on an ARL-Deitert grating spectrograph.

Direct titration in the presence of glycerol, without preliminary ashing or hydrolysis, was employed in 1 instance to determine whether the boric acid was free or combined.

TABLE 2.—*Urinary Excretion of Boric Acid After Single Toxic Doses Given Orally*

| Number of Dogs | Dosage Level, Gm. per Kg. | Mean Percentage of Boric Acid Excreted in Urine | | |
|---|---|---|---|---|
| | | Day 1 | Day 2 | Day 3 |
| 6 | 2.0 | 45 | 12 | — |
| 4 | 1.5 | 45 | 4 | — |
| 1 | 0.4 | 53 | 9 | 2 |
| 2 | 0.2 | 51 | 3 | 1 |

*Phosphorus.*—Urinary inorganic phosphorus was determined by the method of Youngburg,[21] using a Klett-Summerson colorimeter. Serum inorganic phosphorus and lipid phosphorus were also determined by Youngburg's technic.

*Phospholipids.*—The phospholipids of the brain and liver were separated by Folch's procedure [22] and the various fractions examined spectrographically for boron and phosphorus lines.

*Pathology.*—For histopathologic studies the animals were killed by a lethal dose of pentobarbital sodium injected intravenously. Mouse, rat and dog material was fixed in most cases by perfusion with neutral solution of formaldehyde U. S. P. diluted 1:10. A few tissues were preserved by immersion of thin slices. Tissues were embedded in celloidin. Sections of the central nervous system were stained with toluidine blue; other organs were stained with hematoxylin and eosin.

## EXPERIMENTAL RESULTS

*Acute Toxicity.*—(*a*) Determination of L. D. 50: The acute toxicity was determined in rats, mice, guinea pigs and dogs. With regard to the first three species the data were in sufficient numbers for a statistical analysis and the acute toxicity was expressed as the L. D. 50. Forty or more animals were used in each determination. The standard error was calculated according to the method of Litchfield and Fertig.[23] Neutralized boric acid ($p_H$ 7.4) was slightly more toxic than the unneutralized boric acid. The L. D. 50 varies from 1.2 to 3.45 Gm. per kilogram (table 1). Intravenous administration (at a rate of 2 cc. of a 5 per cent solution per minute) was the most toxic. The guinea pig was the most susceptible animal used. The prelethal symptoms in these animals were depression and ataxia (occasionally convulsions), fall in body temperature, violet-red color of the skin and mucous membranes and, in the case of the dog, persistent vomiting and meningismus.

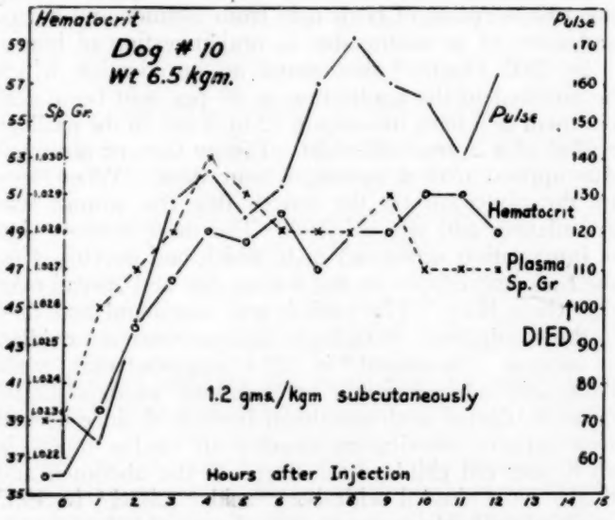


Fig. 1.—Effect of a subcutaneous dose of 1.2 Gm. per kilogram of boric acid on the hematocrit, serum specific gravity and heart rate.

(*b*) Acute Toxicity in Dogs: Dogs were given single oral doses of 2.0, 1.5, 1.0, 0.8, 0.4 and 0.2 Gm. of boric acid per kilogram. Since these doses usually induced emesis, we found that a subcutaneous injection of 30 mg. of morphine had to be given as an antiemetic before the boric acid.

Three of 6 dogs which received 2.0 Gm. per kilogram died within forty-eight hours. This is probably close to the median lethal oral dose. Two of 4 dogs died

19. Wiley, H. W.: Boric Acid and Borax, Circular 15, U. S. Department of Agriculture, Bureau of Chemistry, 1904, p. 27.
20. Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, ed. 5, 1940, pp. 459-460.
21. Youngburg, G. E., and Youngburg, M. V.: Phosphorus Metabolism: A System of Blood Phosphorus Analysis, J. Lab. & Clin. Med. **16**: 158-166 (Nov.) 1930.
22. Folch, Jordi: Brain Cephalin, a Mixture of Phosphatides, J. Biol. Chem. **146**: 35-44 (Nov.) 1942.
23. Litchfield, J. T., and Fertig, J. W.: On a Graphic Solution of the Dosage-Effect Curve, Bull. Johns Hopkins Hosp. **69**: 276-286 (Sept.) 1941.

with a subcutaneous dose of 1.0 Gm. per kilogram; hence this dosage level is probably near the median lethal dose for parenteral administration. Severe toxic symptoms were noted in 4 of 6 dogs receiving 2.0 Gm. per kilogram and in 2 receiving 1.5 Gm. per kilogram. The most obvious sign of intoxication consisted of cyanosis of all mucous membranes, with the skin becoming mottled reddish violet. The legs were rigid and the animals were unable to stand without support. Convulsions of short duration occurred in 2 animals. In 4 dogs the hematocrits, plasma specific gravity and pulse were determined hourly after subcutaneous doses of 1.0, 1.2 and 1.5 Gm. per kilogram. The changes were entirely consistent with the hypothesis that a shocklike syndrome may cause death within twenty-four hours after a single large dose (fig. 1).

Twenty-four hour urine samples were collected, and after varying intervals the tissues were analyzed for boric acid and examined grossly and microscopically for pathologic changes. Approximately 40 per cent of the dose was retained in the body for more than forty-eight hours (table 2). The mean excretion for the larger doses was 45 per cent in the first twenty-four hours and 4 to 12 per cent in the second twenty-four hour period. Thereafter only small amounts were excreted daily. From 1 dog receiving 1.5 Gm. per kilogram orally, hourly blood samples were taken for several hours. Boric acid could not be detected in either erythrocytes, leukocytes or plasma.

(*c*) Effect of Intravenous Injection on Phosphorus Excretion: Dogs operated on to produce an exstrophy of the urinary bladder were given intravenous injections of 400, 300, 250, 200, 100 and 50 mg. of boric acid per kilogram, and urine samples were collected at half hourly intervals for boric acid and phosphorus determinations. In every case there was a sharp rise in boric acid elimination, reaching a peak in one to two hours, followed by a gradual decline. After an initial inhibition lasting for one to two hours a gradual rise in phosphorus excretion occurred, which at six hours exceeded by five times the control value. This increase was most prominent at a dosage level of 250 mg. per kilogram (fig. 2). Plasma lipid and inorganic phosphorus values also were determined at hourly intervals on 3 dogs receiving 200, 100 and 50 mg. of boric acid per kilogram, but no significant changes occurred over a seven hour period.

(*d*) Effect of Acute Intoxication on Blood Electrolytes: In order to ascertain the degree of alteration which moderately toxic doses of boric acid might produce in the electrolytes of the blood stream, 2 dogs which had received 1.0 Gm. per kilogram were bled twenty-four hours after dosing and the blood was subjected to chemical analysis. With the exception of an increased nonprotein nitrogen and, perhaps, concomitant increase in serum potassium in dog 1, no significant change in the blood electrolytes was found.

(*e*) Identification of Excreted Compounds: In an attempt to determine the exact nature of the boron compound excreted, boric acid was titrated directly, without preliminary ashing or hydrolysis, in several aliquots of a single specimen of urine (965 cc.). The quantity found by direct titration accounted for 96 to 101 per cent of the boric acid found by the usual method of ashing. It was concluded that practically all of the boron in this specimen was present as unmodified boric acid. This is in accord with the findings of Wiley[19] that both boric acid and borax are excreted unchanged.

*Chronic Toxicity.*—(*a*) Effect of Repeated Injections on the Cellular Elements of the Blood: Because of the frequent occurrence of persistent anemia in patients with extensive burns, the possible depressant effect of boron on the hemopoietic system was considered. After control hematologic studies, 4 dogs were injected subcutaneously twice daily for forty-five days with a dose of 100 mg. of boric acid in a 5 per cent solution per kilogram. The animals were housed in metabolism cages. Hematologic studies were made twice weekly and the urinary excretion of boric acid was determined daily. Significant change in hemoglobin, erythrocytes or leukocytes did not occur during the period of observation. From the standpoint of possible cumulative toxicity it is significant that the plateau of urinary excretion was not reached until the animals had been on this dosage regimen for fourteen to eighteen days. The mean recovery when the plateau of excretion was reached amounted to 85 per cent of the amount of boric acid injected.

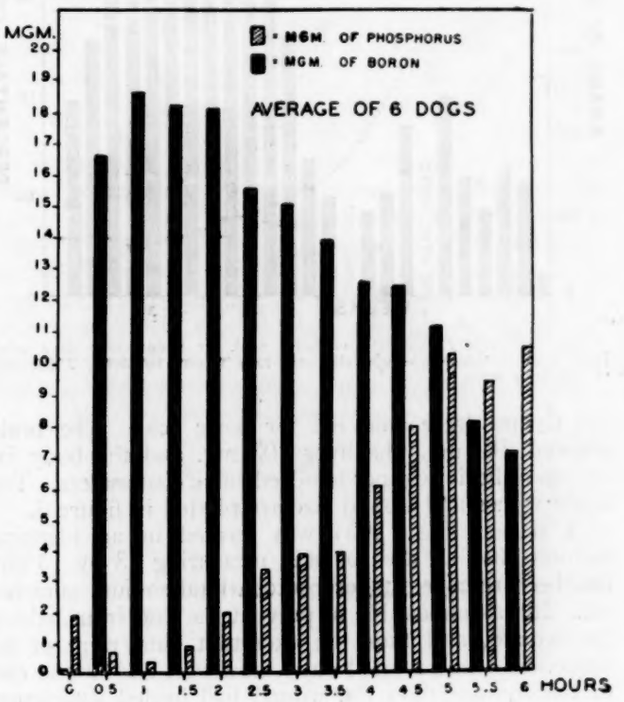


Fig. 2.—Comparative urinary phosphorus excretion after intravenous injections of 250 mg. per kilogram of boric acid.

(*b*) Effect on the Growth of Immature Rats: Five groups of 20 to 24 immature rats each were placed on a standard laboratory diet and given various levels of boric acid in their drinking water and were weighed daily to follow the rate of growth. One-tenth per cent boric acid was without effect on normal rat growth, while 0.25 per cent and all higher levels produced a definite inhibition after twenty to thirty days. The daily fluid intake was constant at 0.14 to 0.12 cc. per gram of rat daily for all three groups. At autopsy no characteristic gross or microscopic pathologic lesions were found. Complete blood counts were done weekly, but no significant change was found in the blood of these animals.

(*c*) Application of 10 per Cent Ointment to Wounds: Under pentobarbital sodium anesthesia a section of skin 13 cm. square was removed from the dorsolumbar surface of dog 204. Fifty Gm. of U. S. P. boric acid ointment was applied daily to the exposed surface and

secured with a pressure bandage. Urine was collected daily for analysis. The area of the wound was measured daily and found to decrease in size. The wound size was expressed in percentage of total surface area as determined by the formula of Benedict.[24] On the twenty-fifth day the animal was killed for autopsy and

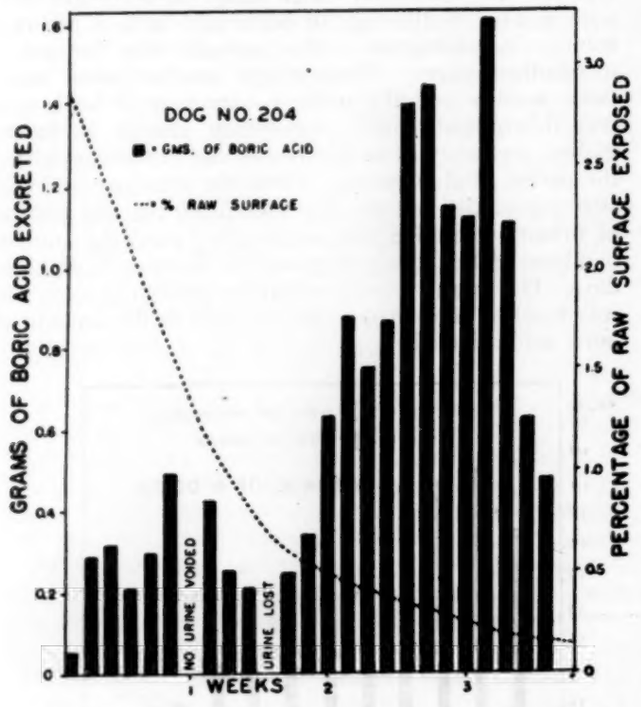


Fig. 3.—Urinary excretion of boric acid for twenty-four days when boric acid ointment was applied daily to a wound involving 3 per cent of the body area.

the tissues were analyzed for boric acid. The brain showed 212 mg., the liver 107 mg. and the body fat 30 mg. of boric acid per hundred cubic centimeters. The urine values and wound size are plotted in figure 3.

A second dog (206) was treated in an identical fashion after an area of skin measuring 13 by 13 cm. had been removed under pentobarbital sodium anesthesia. It was impossible to prevent the dog from licking the wound, and thus the excretion data were of no value. He was treated daily, however, and at the end of twenty-four days the wound had healed sufficiently to discontinue all boric acid dressings. The urine was then assayed daily until a negative turmeric test was obtained on the fourth day. At autopsy the tissues assayed as follows: wound 103 mg., brain 90 mg., liver 73 mg., kidneys 54 mg. and body fat 39 mg. per hundred cubic centimeters and the urine from the bladder was negative.

On a third dog (213) a third degree burn measuring 11.5 by 11.5 cm. was treated with 50 Gm. daily of boric acid ointment under a pressure bandage. Urine values were determined daily for thirty-three days (fig. 4). At the end of this period the brain showed 247 mg., the liver 18 mg., the fat 60 mg. and the wound tissue itself 60 mg. of boric acid per hundred cubic centimeters.

(*d*) Peritoneal Irrigation with Boric Acid Solution: Two dogs were anesthetized with pentobarbital sodium and a 5 per cent boric acid solution was irrigated through the abdominal cavity for a three hour period by means of an inflow cannula in the region of the liver and an outflow cannula in the left lower flank. The rate of flow was adjusted so that 5 cc. per minute entered the cavity. The perfusate was collected hourly, measured and analyzed for boric acid. At the end of three hours the animals were killed and the tissues analyzed for boric acid. The perfusates showed a drop in boric acid content to approximately 1.5 per cent, and on the basis of the total amount recovered 1 animal retained 34.7 Gm. of boric acid, the other 31.0 Gm. (table 3). The average tissue levels were brain 293 mg., body fat 244 mg. and liver 205 mg. per hundred cubic centimeters.

(*e*) Absorption from the Intact Skin: In order to test absorption from the intact skin 2 male subjects wore regulation navy short sleeve undershirts which were saturated and kept moist for an eight hour period with a 5 per cent aqueous solution of boric acid. Repeated analyses of various specimens up to forty-eight hours failed to demonstrate any boric acid in their urine. The turmeric paper test, which is ordinarily sensitive to 1 part in 5,000, was used. In a second experiment boric acid ointment was applied for six hours to the upper half of the body (neck to waist) of 2 normal male subjects. Individual voidings of urine were again negative for boric acid by the turmeric paper test for the entire twenty-four hour period after application of the ointment. In a third experiment 2 subjects, after voiding, immersed their feet to the ankles in a hot saturated (5 per cent) boric acid solution for periods of thirty and sixty minutes respectively. To avoid contamination the subject was not allowed to touch the foot bath at any time. Urine samples at

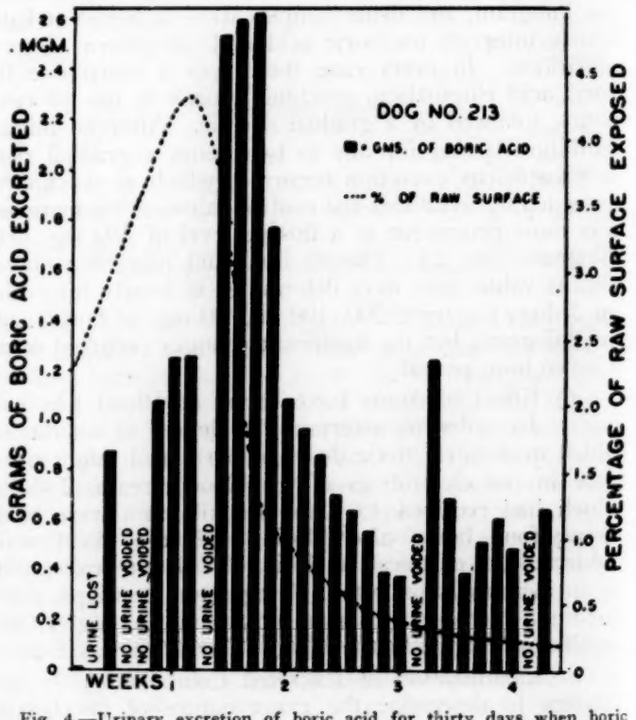


Fig. 4.—Urinary excretion of boric acid for thirty days when boric acid ointment was applied daily to a third degree burn involving 3 per cent of the body area.

one-half, one, three and thirteen hours were negative for boric acid by the turmeric paper test. These samples were alkalized and dried and were found to be almost entirely negative for boron on spectrographic analysis. Only the thirty minute urine samples had very faint boron lines. In the thirty minute urine sample of subject HW the boron line at 2,497 angstroms was

24. Benedict, F. G.: Surface Area Constant in Comparative Physiology, Yale J. Biol. & Med. 4: 385-398 (March) 1932.

slightly less dense than the platinum line at 2,428 angstroms. These densities were reversed in subject CP. Since the only source of platinum was the dish used to ash the urine sample, the amount of platinum and boron in the total ashed specimen can be estimated to be about 10 micrograms. This indicates that the boron in the original urine sample was in the order of 1 part of boron to 10,000,000 parts of urine.

TABLE 3.—*Disappearance of Boric Acid from Perfusate After Peritoneal Irrigation with a 5 per Cent Solution*

| Dog Number | Hours | Cc. of Solution Administered | Gm. of Boric Acid Administered | Cc. of Perfusate Recovered | Percentage of Boric Acid in Perfusate | Gm. of Boric Acid Recovered | Gm. of Boric Acid Retained (by Diff.) |
|---|---|---|---|---|---|---|---|
| 22 | 1st | 300 | 15.4 | 120 | 1.35 | 1.6 | 13.8 |
| | 2d | 300 | 15.4 | 255 | 1.47 | 3.7 | 11.7 |
| | 3d | 300 | 15.4 | 450 | 1.35 | 6.1 | 9.3 |
| | Total | 900 | 46.2 | 825 | .... | 11.4 | 34.8 |
| 23 | 1st | 300 | 15.4 | 21 | 1.06 | 0.2 | 15.2 |
| | 2d | 300 | 15.4 | 420 | 1.64 | 6.9 | 8.5 |
| | 3d | 300 | 15.4 | 430 | 1.84 | 7.9 | 7.5 |
| | Total | 900 | 46.2 | 871 | .... | 15.0 | 31.2 |

TABLE 4.—*Average Boric Acid Content of Organs of 15 Dogs Following Dosage with 2.0 Gm. per Kilogram*

| Organ | Boric Acid Content, Mg. per 100 Cc. |
|---|---|
| Brain | 111 |
| Liver | 91 |
| Body fat | 26 |

(*f*) Tissue Levels and Distribution: In an attempt to determine the distribution of boric acid in the tissues, 3 dogs were acutely intoxicated by the administration of 2.0 Gm. per kilogram, and twenty-four to seventy-two hours later analyses of their tissues were made. These results (table 4) show that the brain, the liver and the body fat in the order named are the three organs highest in boric acid content. This fact was confirmed many times in later experiments.

(*g*) Distribution in Fractions of the Brain: Since the studies thus far tended to confirm the findings of previous workers [25] that a large amount of boron accumulated in the brain, an attempt was made to ascertain its distribution within the brain by separating the white from the gray matter. In a dog highly intoxicated with boric acid, whole brain tissue analyzed 214 mg. per hundred cubic centimeters, while the gray matter, obtained by careful slicing with a razor blade, contained 231 mg. per hundred cubic centimeters. The white matter obtained by careful slicing of the corpus callosum contained 142 mg. per hundred cubic centimeters. The data hence indicate a slight preponderance of boric acid in the gray matter. In an attempt to ascertain which chemical fraction of the brain contained most of the boric acid, fresh brains were fractionated for pure phospholipids according to the method of Folch.[22] The brains of 3 dogs and 1 large hybrid polar bear all previously intoxicated with boric acid were used. Each fraction was tested qualitatively for boron and phosphorus by means of the spectrograph. Only the initial acetone extract of brain showed strong boron lines. Although the alcohol and petroleum ether fractions were purified and tested for boron, as well as the remaining residue, none was found. The acetone fraction was further separated into ether soluble and insoluble fractions. The ether insoluble fraction showed the boron lines but none for phosphorus. This fraction was found to be water soluble. The brain of a control animal was fractionated in the same way and showed very faint traces of phosphorus in the same fraction in which boron alone had occurred in the intoxicated animal.

(*h*) Results of Histopathologic Studies: The major pathologic changes in acute boric acid toxicity in mice, rats and dogs involved chiefly the kidney and central nervous system. In all animals there was glomerular and tubular damage. The former consisted of a change in capillary permeability as manifested by glomerular débris in the glomerular spaces in many of the animals. The latter was more serious and involved sometimes pronounced cellular vacuolization, sometimes cellular shedding into the lumen, and nearly always a rich coagulum in the tubule lumens, which in some cases extended into the ducts of Bellini.

In the central nervous system, pathologic changes consisted largely in the presence of an increased number of small cells with dark, round or irregular nuclei (2-4, fig. 5) and in hyperchromatism and shrinkage of certain nerve cells in the spinal cord (5, 6, fig. 5). The small cells are probably microglia. They were most numerous forty-eight hours after injection and were not present in 2 out of 3 brains at seventy-two hours. The density of these small cells was greater with higher dosage and was not closely related to the concentration of boron in the brain at the time of death (table 5). They occurred in 1 case around blood vessels in all layers of the cortex. In others they seemed to be generally distributed throughout the gray matter of the cortex. In several they appeared clustered around large and small nerve cells, particularly in the deepest layer of the cortex but also in other layers. Sometimes the nerve cells themselves were highly vacuolated, and in one preparation small round cells were present within the cell wall. A moderate reaction took place in the

TABLE 5.—*Relationship of Brain Tissue Reaction to Dosage and Boric Acid Levels*

| Dog No. | Dose, Gm. per Kg. | Days After Dose | Boric Acid in Brain, Mg. per 100 Cc. | Tissue Reaction |
|---|---|---|---|---|
| 127 | 2.0 | 1 | 78 | ++++ |
| 19 | 2.0 | 2 | 190 | ++++ |
| 215 | 1.5 | 2 | 59 | ++ |
| 167 | 1.5 | 3 | 139 | ++ |
| 227 | 1.0 | 2 | 14 | ++++ |
| 229 | 1.0 | 2 | 14 | ++ |
| 230 | 1.0 | 2 | 12 | ± |
| 214 | 0.8 | 2 | 140 | + |
| 202 | 0.4 | 3 | 102 | 0 |
| 203 | 0.2 | 3 | 15 | 0 |
| 157 | 1.5 | 4 | 188 | 0 |

TABLE 6.—*Effect of Polyhydroxyl Compounds and Salt Solutions on the L. D. 50 of Boric Acid Given Subcutaneously*

| No. of Mice | Antidote | Antidote Route | L. D. 50, Mg. per Kg. |
|---|---|---|---|
| 60 | None | ..... | 2,070 |
| 40 | Sorbitol | Orally * | 2,290 |
| 40 | Mannitol | Orally † | 1,900 |
| 30 | Glucose 5% | Subcutaneously | 2,110 |
| 35 | Sodium chloride 0.9% | Orally ‡ | 2,600 |
| 20 | Ringer's 50%, plasma 50% | Intravenously § | 5,300 |

* Two doses 2 cc. 20% in 24 hours.
† Two doses 2 cc. 20% in 24 hours.
‡ Four doses 2 cc. each in 24 hours.
§ Four doses of 1.5 cc. daily for 4 days.

25. Ross and Conway,[15] McWalter,[16] Willson,[10] Forsythe,[26] Potter,[26] Birch,[16] McNally and Rust.[25]

cortex of 1 dog (204) after boric acid ointment had been applied for one month to an area of the body denuded of skin.

The pronounced hyperchromatism and shrinkage of nerve cells in the spinal cord was observed in the dorsal horn, the intermediate cell column and the ventral horn. The degree of reaction was not closely related to the dosage or to the boron content of the brain at the time of death. Moderate changes were noted in dog 204, whose treatment has been described. The absence of reaction in dog 157, which came to autopsy four days after an oral dose of 1.5 Gm. per kilogram indicates that the reaction of nervous tissue to boron probably persists for only seventy-two hours. Other pathologic changes noted were extensive polymorphonuclear reactions in the subdermal connective tissue layers of the skin. The dermal blood vessels were distended with blood, which may account for the erythema seen in man.

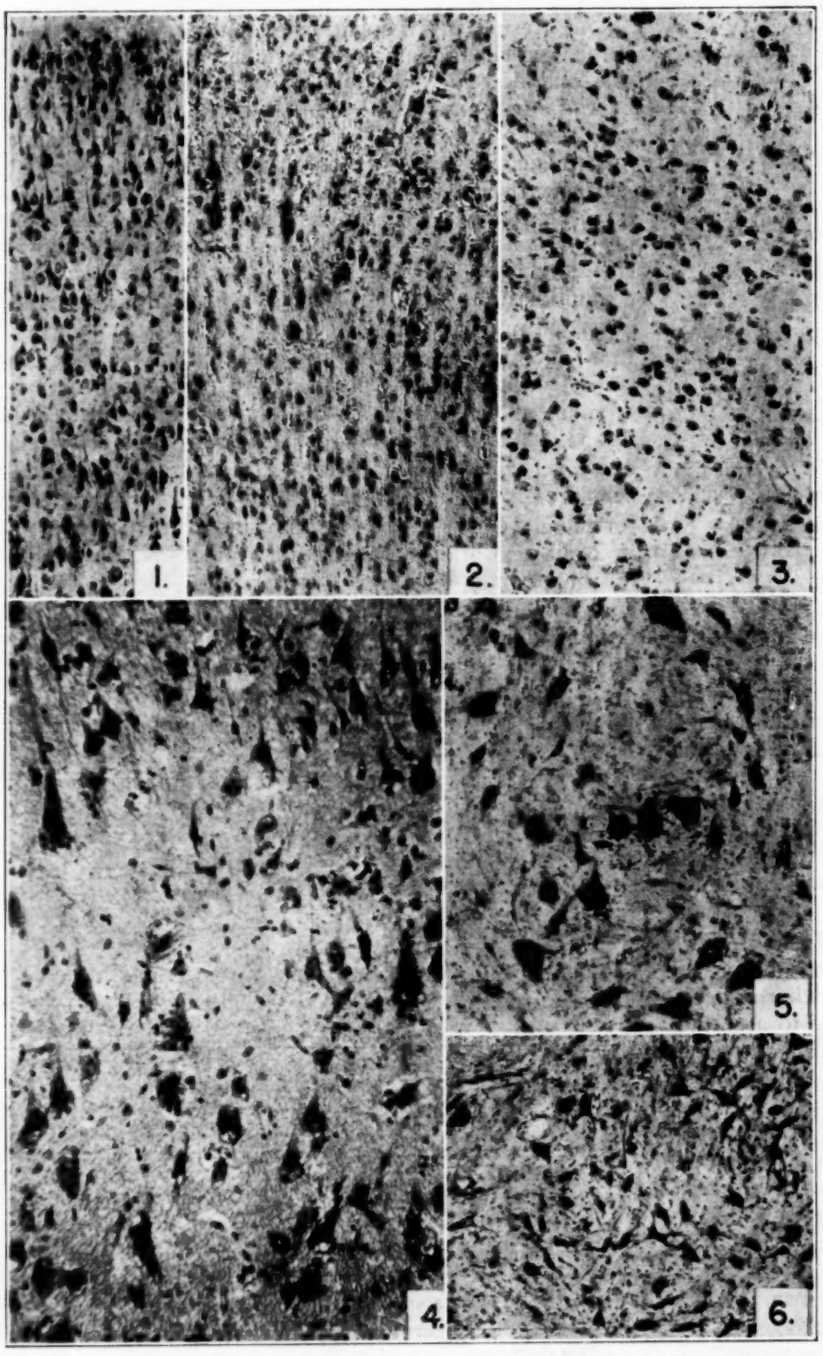


Fig. 5.—Histopathology of the brain and spinal cord following administration of boric acid. Sections of: 1. Cerebral cortex of normal dog × 78. 2. Cerebral cortex of dog 19 × 78. 3. Cerebral cortex of dog 19 × 78. 4. Cerebral cortex of dog 19 × 202. 5. Lumbar cord of normal dog × 78. 6. Sacral cord of dog 215 × 78. All sections from central nervous system fixed with neutral solution of formaldehyde embedded in celloidin and sectioned 20 microns thick. Stained with toluidine blue.

(*i*) Attempts to Antidote Acute Poisoning: Since boric acid combines chemically with polyhydroxyl compounds such as mannitol and glycerol, the administration of these compounds might result in a more rapid excretion (or inactivation) of boric acid and a resultant lessened toxicity. Such an effect should be evidenced by a significant increase in the L. D. 50. Accordingly, mice were injected subcutaneously with toxic doses of boric acid, and various polyhydroxyl compounds were given orally or subcutaneously in the same solution as the boric acid. No antidotal effect, however, was found with any of these compounds. Isotonic solution of three chlorides (combined with plasma or bovine albumin) was strikingly effective as an antidote if given repeatedly in large intravenous doses. These data are summarized in table 6.

## COMMENT

With respect to the absolute dosage of boric acid tolerated by the mouse, rat, guinea pig and dog one can state that boric acid is relatively nontoxic. Death is probably due to a combination of vascular depression and central nervous system intoxication. The fact that repeated intravenous injections of isotonic solution of three chlorides and plasma will allow the mouse to tolerate 2.5 times the usual L. D. 50 of boric acid indicates that the most important antidotal measures are those which will counteract circulatory depression and aid in urinary excretion.

The increased excretion of phosphorus after intravenous injections may be entirely incidental to tissue injury or it may be due to the chemical release of phosphorus from some compound which has a greater affinity for boron. In support of the latter hypothesis is the occurrence of this phenomenon at a relatively low dosage, the disappearance of the phosphorus lines from the spectrum of that fraction of the brain which absorbs the boron, and the previous findings of Wiley[19] that phosphorus metabolism is definitely disturbed in man during a period of boric acid or borax administration.

The failure of boron to intoxicate the hemopoietic system probably indicates that no portion of the severe anemia which frequently accompanies extensive burns is caused by the treatment of the burns with boric acid ointment.

While the evidence for cumulative action is not incontrovertible, many of the isolated observations in this study indicate that boric acid is definitely a cumulative

poison. These are (1) the long period (fourteen to eighteen days) needed for urinary excretion to reach a plateau, (2) the relatively low forty-eight hour excretion (60 per cent), (3) the characteristics of the urinary excretion curve when boric acid ointment is applied to burns or wounds, (4) the persistence of appreciable amounts of boric acid in the brain and liver of dogs for as long as four days after stopping the daily dose and (5) the accumulation of greater amounts of boron in the brain than that which occurs in the treated wound.

Because of the phosphorus content of phospholipids and the fact that one of the cephalins is known to contain inositol and hence might be expected to absorb boric acid, considerable care was taken to separate the various fractions of the brain. The boron, however, was entirely separated in the first extraction procedure used; namely, drying the brains with acetone. Since boron is also found in large amounts in the body fat, one can postulate that it probably occurs as boroglycerate. Proof of this assumption must await further detailed studies.

The failure of boric acid to appear in the urine when administered as a saturated solution or ointment to the torso of the normal human subject indicates that absorption through the intact skin is negligible. These results are not in agreement with those of Kahlenberg,[26] who detected boric acid in the urine fifty-five to sixty seconds after he immersed his feet in a warm saturated solution. Ochsner [27] also states that boric acid is absorbed through the intact skin. Since three types of experiments designed to favor skin absorption gave negative results by both the turmeric paper test and spectrographic analysis we must conclude that, if skin absorption occurs, the quantity of boron thus taken into the body is negligible and will not result in systemic toxicity.

The degree of expected absorption of boric acid when a saturated solution is used to irrigate a closed cavity has been accurately determined in these studies. Under favorable circumstances the absorption may be as high as 75 per cent of that contained in the irrigating fluid. This definitely prohibits the use of boric acid for that purpose. The washing of granulation tissue for any length of time is probably also highly dangerous.

Boron can be added to that group of elements which are known to affect the central nervous system. These include lead, manganese and arsenic. Compared to these intoxicants boron is much quicker in its action and recovery is also more prompt and apparently more complete. The use of boron as an antiepileptic,[28] which has been advocated from time to time, is probably in accord with the degree of tissue damage attained, but this assumption would have to be confirmed by functional studies in boron intoxicated animals.

## SUMMARY

1. Boric acid is absorbed in toxic quantities from ointments applied to burned areas or to wounds involving loss or damage to large areas of skin.

2. When a 5 per cent boric acid solution is used to irrigate cavities, most of the boric acid is absorbed by the tissues.

3. While boric acid is not toxic when administered in a single large dose, repeated doses result in accumulation in the brain, liver and body fat.

4. The boron occurs in both the white matter and gray matter of all parts of the central nervous system and in the peripheral nerves. The spinal cord and gray matter of the cerebrum contain the highest amounts.

5. The liver is only slightly affected histologically by chronic poisoning. The kidney shows tubular degeneration, while the brain and spinal cord show neuronophagia and hyperchromatosis. The skin shows polymorphonuclear infiltration and vascular engorgement.

6. As little as one third the median lethal dose, or treatment of a burn involving only 4 per cent of the surface area of the body with U. S. P. 10 per cent ointment, will produce pathologic changes in the central nervous system.

7. When repeated daily doses as small as 200 mg. per kilogram are given subcutaneously, fourteen to eighteen days are required before urinary excretion reaches a plateau. This, together with the fact that boric acid can still be found in the brain of animals four days after discontinuation of a series of doses, indicates cumulative action.

8. The growth of immature rats is not influenced by 0.1 per cent of boric acid in the drinking water, but a level of 0.25 per cent retards normal growth after twenty days.

9. The data do not provide any evidence of a depressant action of boric acid on the blood forming organs.

10. A definite increase in urinary phosphorus excretion occurs after intravenous doses of boric acid.

11. The boron found in the brain is not combined with phospholipids or cholesterol but is probably present in some simple combination with glycerol or other polyhydroxyl compounds.

12. Death is due to a shocklike syndrome when large doses are given. If moderate dosage is given over a period of several days, death may result from inanition due to convulsive tremors and meningismus. When intravenous fluids are given to prevent early deaths, some animals develop anuria at 2.5 times the untreated median lethal dose.

13. Polyhydroxyl organic compounds such as mannitol, glucose or glycerol are not antidotal to boric acid. Large intravenous doses of isotonic solution of three chlorides and plasma definitely antidote the toxicity.

## CONCLUSION

Boric acid, whether applied in the form of an ointment or a saturated solution to extensive wounds, is a cumulative poison. The weak antiseptic value of boric acid suggests that for medicinal use other more active and less potentially harmful therapeutic agents should be employed.

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## ABSTRACT OF DISCUSSION

DR. CHARLES G. BARNUM, Groton, Conn.: I am reporting the boric acid poisoning of 20 newborn infants in our hospital at New London, Conn. The poisoning was the sequel of the issuing of granular boric acid powder, which looks like dextrose powder, in a jar plainly labeled "Dextrose." When the jar was returned to our formula room the boric acid was made up in isotonic solution of sodium chloride instead of dextrose in saline solution to be used as a prelacteal feeding. The first noted effect came in one infant within eight hours of the time the solution was taken. There was vomiting, diarrhea and a rapidly progressive prostration, which went on to death in about thirty-six hours from the time the first dose was taken. Four other youngsters succumbed. The first clinical effect was vomiting, but the most striking symptom was a tremendous irritation of the central nervous system. The appearance was that of severe meningitis with retraction of the head, opisthotonos,

26. Kahlenberg, Louis: On the Passage of Boric Acid Through the Skin by Osmosis, J. Biol. Chem. **62**: 149-156 (Nov.) 1924. Kahlenberg, L., and Barwasser, N.: On the Time of Absorption and Excretion of Boric Acid in Man, J. Biol. Chem. **79**: 405-408 (Oct.) 1928.
27. Ochsner, E. H.: Biochemistry of Topical Application: Use of Boric Acid in Septic Infections, J. A. M. A. **68**: 220 (Jan. 20) 1917.
28. Verjaal, A.: Boron as an Antiepileptic, Nederl. tijdschr. v. geneesk. **83**: 1226-1233 (March 18) 1939.

double Kernig sign, Babinski reflex and rather evident spastic deviation of the eyes. The temperature curves were nearly flat. The urine was scanty and contained little albumin. The amount of prostration was remarkable, with rapid loss of weight due to diarrhea and the failure to take any reasonable amount of fluids. In treatment the fluid requirement was made up with a mixture of isotonic solution of sodium chloride and 5 per cent dextrose solutions given by hypodermoclysis. In the more severely poisoned there was intense generalized redness of the skin, after which the surface came off, as though the youngsters had been superficially burned. The less severely poisoned showed a macular eruption followed by desquamation. The postmortems seemed to indicate that there was a similar extensive inflammation of the mucous membranes. One youngster who survived a good deal longer than the others eventually died of the boric acid poisoning, even though the chemical analysis of the organs showed that the boric acid apparently had been entirely excreted before death. Even to the last the clinical picture was similar to that presented by those who died earlier. The area of exfoliation covered practically the whole surface of the body, even the bottoms of the feet.

Dr. Henry N. Harkins, Baltimore: In my practice of surgery I see no absolute indication for the use of boric acid in any form whatever. The reports made here today and the discussion bear out once again the toxic dangers of this substance. Would it not be in order to have this section send a recommendation to the Council on Pharmacy and Chemistry that it investigate the possibility and advisability that boric acid be entirely eliminated from all hospitals?

Dr. Lincoln S. Opper, Norwich, Conn.: There were five deaths in connection with the cases of boric acid poisoning at the New London Hospital. I performed autopsies in 4 cases. Three of the examinations were on 6 to 8 day old infants who had received varying amounts (10 to 13 Gm.) of boric acid in the form of a 5 per cent solution over a period of four days and who succumbed one or two days after the error was recognized and the feedings terminated. The fourth infant lived for sixteen days, having survived the final ingestion of boric acid by eleven days. At autopsy all of the infants showed a more or less extensive generalized rash in the nature of a red exfoliative dermatitis. This has been frequently described in the literature. In the first 3 infants fresh petechial and ecchymotic hemorrhages were noted in the pleural and epicardial surfaces as well as within the thymic tissue. This was thought to be related to anoxia. Focal hemorrhages of considerable size involved the pulmonary parenchyma. Despite superficial erosions of the tongue and despite a diffuse redness of the esophageal mucosa and a few focal areas of fresh hemorrhage in the submucosa of the bowel, the gross changes in the gastrointestinal tract were certainly not impressive. Microscopically the degree of epithelial degeneration and regeneration, particularly of the small intestine, was much more striking. The upper part of the gastrointestinal tract was characterized by an extensive hemorrhagic esophagitis with necrosis and sloughing of large patches of epithelium. In the small intestine, and to a lesser degree in the colon, the cells of the glandular epithelium were very large, with hyperchromatic and bizarre shapel nuclei containing large and prominent nucleoli. Mitotic figures were very numerous. The hemorrhagic cystitis, which was also found in the first 3 cases and which has been commonly described in boric acid deaths, resembled in every way the involvement of the esophagus. The microscopic findings in the liver and kidney were rather disappointing in that the amounts of fat within the cytoplasm of the hepatic and tubular epithelial cells were relatively small and could scarcely be considered pathologic. The brains were all decidedly congested and showed mild cerebellar pressure areas. Blocks of cerebral tissue are being embedded in celloidin to be stained by various neuropathologic technics. In the fourth infant, whose death occurred on the sixteenth day, none of the lesions already described in the gastrointestinal tract and bladder of the first 3 were found. The exfoliative dermatitis was still present in wide distribution, and a bilateral focal pneumonia was noted as the cause of death. Quantitative determinations on the brain or liver of each case revealed 0.52, 0.558 and 0.78 Gm. respectively of boric acid per hundred grams of tissue in the first 3 infants. In those deaths of 6 infants resulting from the accidental ingestion of boric acid which occurred in a Chicago hospital in 1927 the amounts of boric acid recovered from the brain and liver represented approximately a third of our figures. However, the amounts of boric acid taken (saturated solution mistaken for distilled water) were correspondingly smaller. No evidence of boric acid could be demonstrated in the liver of the fourth infant, indicating that the survival time had allowed for complete excretion of the drug.

Lieutenant Carl C. Pfeiffer, U.S.N.R.: Dr. Barnum of the New London Hospital had 21 severely poisoned infants, and it can be stated definitely that the mortality in this series of 21 infants was much less than in the instances previously described. Pharmacologically we are definitely handicapped in that there is no animal which has a skin like that of the human being. The skin effects from boric acid poisoning are greater in the case of man, and we do not see as severe pathologic changes in animals. We were glad to have the confirmation of the relative lack of liver damage, which we also found in the animals. We can second the pertinent suggestion of Dr. Harkins that boric acid be discontinued in medicine.

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# TREATMENT OF NEUROSYPHILIS WITH PENICILLIN

## A PRELIMINARY REPORT

DOUGLAS GOLDMAN, M.D.
CINCINNATI

The effectiveness of penicillin in the treatment of syphilis has been clearly demonstrated in early cases by Mahoney [1] and in later cases by Stokes and his group.[2] Early results indicated definite therapeutic benefit. It is to be expected that the drug which is so clearly effective against the treponeme in early cases will be effective as well in the late manifestations of the disease. Advantages which are to be expected in the use of this substance are ease of administration, diffusibility and lack of any serious toxic effects. In this respect it differs widely from all the arsenicals which are in common use.

At Longview State Hospital there is a large group of cases of neurosyphilis available for treatment practically at all times. The admission rate for cases of syphilis varies between 16 and 25 per cent. The average yearly admissions, therefore, for neurosyphilis will be approximately 100 cases. These offer a rather unusual opportunity to study the effects of this very interesting drug in such cases.

For the purpose of the study it was decided to use only patients with dementia paralytica who had unquestionable and typical serologic, spinal fluid and clinical manifestations. Patients with less than typical findings were excluded and were treated with the more common methods. The first 18 cases are presented in this report. In addition a small group of patients with tabes dorsalis was available. Their treatment will be described separately because of its apparent importance in spite of the small number of the group treated. No definite technic for the use of penicillin in syphilis has as yet been established, so this study was initiated with the purpose of trying several technics to determine what results may be reasonably expected from the

From Longview State Hospital, Dr. E. A. Baber, superintendent.

This is the initial report of a project for treatment of neurosyphilis with penicillin organized in Ohio State mental hospitals of the Ohio Department of Public Welfare, Dr. F. Tallman, commissioner of mental diseases.

1. Mahoney, J. F.; Arnold, R. C.; Sterner, B. L.; Harris, A., and Zwally, M. R.: Penicillin Treatment of Early Syphilis, J. A. M. A. **126**: 63-67 (Sept. 9) 1944. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis, Am. J. Pub. Health **33**: 1387-1391 (Dec.) 1943.

2. Stokes, J. H.; Sternberg, T. H.; Schwartz, W. H.; Mahoney, J. F.; Moore, J. E., and Wood, W. B.: The Action of Penicillin in Late Syphilis, J. A. M. A. **126**: 73-78 (Sept. 9) 1944.

methods tried and what modification of the methods tried should be further studied.

In the treatment of the dementia paralytica patients thus far two methods of management were followed. In the first group the patients were given penicillin by a combination of intrathecal and intramuscular injection. The routine established for the purpose of study was as follows: For six days the patients received intrathecal penicillin: on the first two days 10,000 units each day, and on the subsequent four days 20,000 units each day. The technic of making the intraspinal injection, we believe, is of some importance. The penicillin as obtained on the market was dissolved to contain 5,000 units per cubic centimeter; i. e., the 100,000 units was dissolved in 20 cc. of saline solution in the vial in which the penicillin was purchased in the usual manner. Then 2 or 4 cc. of this solution was drawn into a 20 cc. syringe. After the spinal puncture was made and a specimen of spinal fluid for examination was obtained, the syringe was attached to the spinal needle and spinal fluid was drawn slowly to the 20 cc. mark on the syringe. The syringe was then detached and the spinal fluid and penicillin solution thoroughly mixed. Then the mixed penicillin and spinal fluid was reinjected slowly, approximately five minutes being taken

TABLE 1.—*Results of Treatment with Intraspinal and Intramuscular Penicillin in Dementia Paralytica*

| Name | Age | Sex | Color | Duration of Mental Symptoms | Previous Treatment | Physical Condition on Admission | Result * |
|---|---|---|---|---|---|---|---|
| L. S. | 31 | ♂ | Black | 3 mo. | Irregular | Fair | A |
| J. T. | 53 | ♀ | White | ? | ? | Fair | C |
| J. C. | 38 | ♂ | Black | 6 mo. | ? | Poor | C |
| J. C. | 44 | ♂ | White | 1 yr. | None | Very poor | Died |
| R. C. | 35 | ♂ | Black | 3 mo. | Irregular | Good | B |
| L. H. | 46 | ♂ | White | 1 yr. | Irregular | Poor | B |
| L. K. | 36 | ♂ | White | 6 mo. | None | Fair; tbc. | A |
| A. A. | 52 | ♂ | White | ? | ? | Poor | — |
| J. R. | 38 | ♂ | White | 6 mo. | None | Very poor | Died |
| E. B. | 51 | ♀ | White | 8 mo. | None | Fair | A |
| E. C. | 42 | ♀ | White | 4 yrs. | Irregular | Fair | C |

* In the tables A is used to designate apparent recovery; B, much improved; C, improved and D, unimproved.

for the injection. The procedure was repeated daily as outlined. During the same period the patient received intramuscular injections of penicillin into the gluteal muscles, 20,000 or 25,000 units being injected every four hours. A total of 900,000 units of penicillin, including the intraspinal injection, was given with the first course. One month after this another series of intramuscular injections alone was given totaling 1,000,000 units, so that the patients received a total of 1,900,000 units altogether. Spinal fluid examinations were made daily during the period of intraspinal injections, one week later and then at the end of thirty, sixty and ninety days to determine changes in the spinal fluid. The patients were not released from the hospital for ninety days, and following this it is projected to observe the patients at three month intervals, including blood and spinal fluid examinations to determine the lasting effectiveness of this form of treatment.

The idea of using intraspinal treatment for neurosyphilis is obviously not new. Swift and Ellis [3] used serum from the patients themselves, drawn immediately after injection of the arsenical. Their method, however, seemed unnecessarily hazardous and burdensome, in spite of frequent brilliant results. The use of penicillin in this manner, on the other hand, is very simple, rapid and completely safe as medical procedures go.

3. Swift, H. F., and Ellis, A. W. M.: The Direct Treatment of Syphilitic Diseases of the Central Nervous System, New York M. J. 96: 53-55, 1912.

The second group of patients with dementia paralytica was treated with a combination of artificial fever and intramuscular injections of penicillin. The patients were given the routine type of fever treatment used in our hospital, administered by means of the diathermy induction current and an insulating blanket. Temperature records were kept on a recording type of electrical thermometer during the treatment. A total

TABLE 2.—*Results of Treatment with Fever and Penicillin in Dementia Paralytica*

| Name | Age | Sex | Color | Duration of Mental Symptoms | Previous Treatment | Physical Condition on Admission | Result |
|---|---|---|---|---|---|---|---|
| J. B. | 24 | ♂ | White | 3 mo. | Heavy | Good | B |
| K. J. | 33 | ♂ | Black | 1 yr. | Irregular | Poor | C |
| C. P. | 41 | ♂ | White | 6 mo. | None | Fair | B |
| M. W. | 34 | ♀ | White | 1 mo. | Irregular | Good | A |
| G. D. | 60 | ♂ | White | 1 yr. | None | Fair | A |
| M. S. | 58 | ♀ | Black | 2 yrs. | Irregular | Fair | B |
| C. G. | 42 | ♂ | White | 1 yr. | Irregular | Fair | C |

of approximately thirty hours of fever was given to each patient. This consisted of three sessions of two and one-half to three hours at 105 F. or over each week for a period of four weeks. After the third or fourth fever treatment penicillin 20,000 or 25,000 units every four hours to a total of 1,000,000 units was given. After one month 1,000,000 units was injected in a similar manner without further fever treatment.

Observations made on the patients receiving intraspinal treatments are of some interest. In spite of the large doses of penicillin injected intrathecally no serious local manifestations from the treatment were observed. Eight of 10 patients had fever on one or more days following the intrathecal injection. In every instance the temperature returned to normal before the treatment was completed and remained normal apparently in spite of continued injections of large doses of penicillin. Pleocytosis in the spinal fluid was observed in almost every instance. This was always a transient effect of the drug, although in some instances it was very pronounced. I believe that the proper interpretation of these changes is to consider them a manifestation of so-called therapeutic shock rather than an effect of the penicillin itself. It is well known that any foreign substance, serum or drug will produce increase in the number of cells in the spinal fluid,[4] yet repeated injections of serum will produce repeated

TABLE 3.—*Results of Treatment with Intraspinal Penicillin in Tabes*

| Name | Age | Sex | Color | Duration of Symptoms | Previous Treatment | Physical Condition on Admission | Result |
|---|---|---|---|---|---|---|---|
| C. S. | 38 | ♀ | White | 4 yrs. | Heavy | Poor | A |
| L. P. | 38 | ♂ | White | 2 yrs. | Heavy | Fair | C |
| A. E. | .. | ♀ | White | Over 10 yrs. | Heavy | Good | A |
| A. B. | .. | ♂ | White | 3 yrs. | Heavy | Good | C |

increase in cells in the spinal fluid, whereas the injection of penicillin produced only temporary increase which diminished in spite of continued administration of the drug by this route. Similarly the fever seems more fairly ascribed to therapeutic shock than to the effect of penicillin.

All of the patients receiving intraspinal injections of penicillin were allowed up and about the ward except while they had fever and except those patients

4. Goldman, Douglas: Serum Meningitis, Arch. Path. 9: 1027-1037 (May) 1930.

who were too weak and physically disabled from their illness to be allowed this privilege. It is an interesting observation that none of the patients suffered from the so-called spinal puncture headache.

The patients who received fever and penicillin showed no toxic effects whatever from the penicillin. No febrile reaction was observed and there was no evidence of increase in spinal fluid cell counts one week after the treatment. The management of the fever was in no way affected by the use of the penicillin. It seems that the administration of three or four fever treatments before injection of penicillin is an effective means of avoiding therapeutic shock.

The patients used for this study were typical of the state hospital admissions for dementia paralytica. All showed recognizable mental symptoms. They were all in an advanced stage of the disease, many had received irregular treatment over varying periods previous to admission and some had received no treatment at all, as indicated in the summarizing tables. The treatment was administered to 2 patients who were practically moribund, not in the hope of producing benefit but to test the safety of the method. One patient with far advanced tuberculosis who had had a therapeutic pneumothorax maintained for over one year was included in the series.

The 2 aforementioned patients died within ten days following the first series of intraspinal treatments. These had been in a state of pronounced physical and mental deterioration before treatment was started and were to be considered tests of safety rather than hopeful attempts at treatment. This in itself is an interesting point, since among a group of deteriorated patients suffering from dementia paralytica 10 to 20 per cent may be expected to die within three months following admission to a state hospital, regardless of their manner of treatment. Some degree of clinical improvement is manifested in practically every one of the remaining patients. Eight cases show evidence of rapid remission which can be expected to lead to complete recovery within a short time. Nine others have shown within the period of observation improvement of varying degree which is sufficiently definite to justify an optimistic outlook for eventual recovery. The only complete failures in the series were the patients who failed to survive. The results in the patients treated with fever and penicillin are practically similar to those in the patients treated with the combination of intraspinal and intramuscular penicillin. A number of the latter, however, were certainly in no fit condition to have fever treatment and would have been considered hopeless for any other means of therapy than the one employed.

Whether this method of treatment with the doses outlined is to be considered the most effective procedure must be settled by longer observation. It is quite likely that the ideal method of treatment of such patients will be by means of multiple procedures, perhaps larger amounts of penicillin and fever. Arsenicals and bismuth are being withheld from this group of patients because (1) improvement seems adequate or better thus far and (2) the results of the single drug should not be obscured.

### TABES DORSALIS

The treatment of the patients with tabes dorsalis is particularly interesting. Four such patients were treated, 2 from the hospital and 2 from private practice.

Two of the patients showed as their chief manifestations tabetic crises with pronounced abdominal and other sensory root symptoms. In 1 patient the crises were of such severity that she had been committed to the hospital not for syphilis but for a deep suicidal depression which resulted from the severity of her pain. These recurred at intervals of approximately thirty days and lasted from five to twelve days more or less in each bout. The other patient was one who had had more or less chronic pains which had become unendurable for a long period. Both of these patients had had intense antisyphilitic treatment over a long period and were considered well otherwise.

The other 2 patients with tabes were patients who showed typical motor manifestations of ataxia of the lower extremities. These patients had also received large amounts of treatment by means of fever, arsenicals and bismuth, with apparent arrest of the symptoms but certainly inadequate improvement in the chief manifestation of the disorder.

The patients suffering from tabes were treated with intrathecal penicillin only. The method of administration was the same as that used for the dementia paralytica patients. Six daily injections were made with a total of 100,000 units of penicillin. No other treatment was given at the same time. Patient A. B. was further treated with aldarsone beginning one week after the treatment.

The period of observation on the ataxic patients is considered too brief as yet to be conclusive. A certain amount of definite improvement, however, is clearly manifested in at least 1 of these. The patients who suffered tabetic crises, however, showed improvement that was almost immediate and is apparently of an enduring nature. The patient with the worst pain, who had been suicidal because of its severity, has had no recurrence of symptoms for a period of approximately three months in spite of the occurrence of acute pyelitis during this period. The pyelitis responded in the usual way to sulfonamide drugs and was associated with no excessive pain. This woman's personality has changed to one of normal warmth and brightness from its previous distracted depression. The other patient has also enjoyed remarkable relief from pain. The improvement is less striking only because the pain was not so dramatic to begin with. In these patients also the period of observation is too brief to be conclusive for the establishment of a technic, particularly with regard to dosage and frequency of administration of the drug.

### CONCLUSION

1. Eighteen patients with dementia paralytica and 4 patients with tabes dorsalis were treated with penicillin.

2. Patients with dementia paralytica were divided into two groups, one of which was treated with a combination intraspinal and intramuscular penicillin, the other with fever and intramuscular penicillin alone.

3. With only 2 exceptions definite clinical improvement occurred in all of the patients in this group. Some of these are apparently recovering rapidly from their disease.

4. The spinal nerve root pains of tabes are apparently rapidly relieved by intraspinal administration of penicillin.

5. Only 2 patients of the entire series died within a short period after the treatment, and these were practically moribund with strong physical and neurologic evidence of deterioration previous to treatment.

6. Early results are sufficiently favorable to justify continued study of the treatment of neurosyphilis with penicillin by various technics.

# THE LOW AGGLUTININ TITER OF BOTH SMALL AND LARGE POOLS OF PLASMA

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It is well known that when plasmas obtained from individuals belonging to the different blood groups are pooled there is evident neutralization of the agglutinins in the pooled plasma. This neutralization of the agglutinins occurs between A and B agglutinogens present in solution in the plasma from groups A, B and AB and the anti-A and anti-B agglutinins from groups O, A and B.

The agglutinin titers in pooled plasma are believed to be sufficiently low so that pooled plasma can be administered intravenously in large amounts to individuals of any blood type without fear of causing serious reactions from possibly incompatible agglutinins.[1] This is borne out by an extensive, worldwide experience by a great number of physicians in the therapeutic intravenous use of pooled plasma.

However, when this investigation was started there were no publications of the determination of the agglutinin titers in large numbers of pools of plasma as they are being prepared for use by the armed forces and in civilian practice. In fact, there was no generally accepted single technic for isoagglutinin titration. Some observers read the tests macroscopically and some with low power microscope magnification. Some carry out the tests on regular microscope slides, some in test tubes. Some centrifuge the test tubes before reading, some do not. The time factor before reading the test varies from a few minutes (with the centrifuge technic) to two hours. Temperature varies also, although most tests are carried out at "room temperature." Consequently it has been impossible to compare titrations by different workers using different technics, and this will continue until a standardized method is adopted by all.

At present there appears to be a trend for every one to use a macroscopic test tube technic similar to that described here. This method is simple, requires only simple apparatus, such as test tubes and pipets, is accurate and can be performed by any competent laboratory technician. It is the method of choice when only a few plasmas or serums must be titrated. It becomes arduous when large numbers of samples are to be examined, and for large scale use the large slide method is to be recommended.

This report is based on the determination of the anti-A and anti-B agglutinin titers in liquid samples of 1,354 pools of plasma. (Most of these pools represented by these samples were shell frozen and dried.)

Nine hundred and ninety-eight samples were obtained from eight processing laboratories during their routine preparation of pools of plasma for the armed forces, from citrated blood obtained through the Blood Donor Service of the American Red Cross. One hundred and forty-two samples were obtained from the Surgical Physiology Division, Army Medical School, and 209 samples from the Blood and Plasma Department, Naval Medical School.

These samples were obtained at random as the plasma was being processed, or occasionally samples from every fifth or tenth pool were taken. In the processing laboratories, therefore, these represent random samples from an extremely large number of pools, and a very considerable number of pools from the Surgical Physiology Division, Army Medical School, and the Naval Medical School. There also was no selection of blood groups of the individual plasmas which went into each of these pools; the plasmas were pooled as they came to the laboratory.

## METHODS

The titrations were carried out by a large glass slide method,[2] and the readings were made macroscopically. This method was checked repeatedly with the test tube method as used by the Surgical Physiology Division, Army Medical School,[3] and macroscopic readings with both were found to check practically always within one dilution. Duplicate tests with both methods also checked practically always within one dilution. This is the limit of accuracy of both methods.

With this large slide method one can also use an end point by examination under the low power of the microscope. This modification is described so that it may be used for comparison with other methods using a similar end point. We have compared this with Davidsohn's method,[4] in which the end point is determined under the low power of the microscope, and found the titers by both methods to check within one dilution. The low power microscope titers are always one or two dilutions higher than the naked eye titers, and this should be taken into consideration in comparing the two.

However, we recommend that only the macroscopically determined titer be utilized, since it checks well with the test tube method, also read macroscopically.

## LARGE GLASS SLIDE METHOD FOR DETERMINING THE AGGLUTININ TITER[5]

1. The A and B cells used in determining the titer of a serum must be of average sensitivity. This is determined by testing the cells of several individuals against a serum or plasma of low titer, using ascending dilutions of the low titer serum. Dilutions of the serum should be in arithmetical progression (1:10, 1:20, 1:30 and so on). It will be found that the end point will vary with the same serum with different cells. The spread may be, for example, from 1:10 to 1:50. In such a case cells showing an end point at approximately 1:30 may be considered of average sensitivity.

A sufficient amount of blood may be taken from a satisfactory donor for one week's work and placed in enough sodium citrate solution to prevent clotting. These cells must be kept refrigerated and a sufficient amount for the day's work removed each morning and washed three times with an 0.85 per cent solution of sodium chloride.[6]

From the American Red Cross Blood Donor Service and the Public Health Research Institute of the City of New York, Inc.

1. Thalhimer, W.: Intravenous Injection of Pooled Normal Plasma or Serum: Is It Dangerous? J. A. M. A. **120:** 1263-1267 (Dec. 19) 1942.

2. Perfected at the Connaught Laboratories.

3. Lozner, E. L., and Newhouser, L. R.: Preservation of Normal Human Plasma in the Liquid State: Studies on Isohemagglutinin Titers, J. Clin. Investigation **23:** 361-363, 1944.

4. Davidsohn, I.: Test for Infectious Mononucleosis, Am. J. Clin. Path. (Tech. Supp.) **2:** 56-60, 1938.

5. This method can be used with accuracy for determining blood types in large numbers of individuals.

6. Usually fresh cells from the same individuals were used.

A 1 or 2 per cent suspension of the cells in an 0.85 per cent solution of sodium chloride should be used for the titration.

2. Final dilutions of the plasma or serum should be made as follows: 1:10, 1:20, 1:40, 1:80, 1:160 and so on (or 1:2, 1:4, 1:8 and so on).

3. The dilutions recorded should be actual dilution of the serum used in the individual tests.

4. The same pipet is used throughout a single test. The most convenient is an eyedropper with a rubber nipple. This will insure all drops being of the same size. Care must be taken to rinse the pipet thoroughly with an 0.85 per cent solution of sodium chloride each time a different solution or different dilution is used.

5. The tests are performed on large plate glass slides, 4 by 10 inches in size, ruled off in 1 inch squares with a wax pencil. The drops of plasma or serum and the suspension of cells are placed in the center of each square. The mixture on each square consists of one drop of original or diluted plasma or serum, one drop of a 1 per cent suspension of cells that have been washed three times in isotonic solution of sodium chloride and one drop of isotonic solution of sodium chloride. The addition of the drop of saline solution has been found to increase the accuracy of the test and prevents drying before the tests are read. (We have corrobrated the findings of Wiener that this small amount of dilution caused by the additional drop of saline solution does not influence the determination of the titer of the plasma. The amount of agglutinin added is the determining factor, and it takes at least six or seven times dilution with added saline solution to influence the degree of agglutination in each individual test.)

The slides are then placed on a mechanical shaker [7] and the rheostat set to give a rotating motion at the rate of about 120 movements to the minute. The slides are left on the shaker for thirty minutes and then taken off and placed on a table for five minutes before being read. The readings are made by naked eye and can be made by low power microscope. (The smooth surface of the plate glass permits more accurate determination of the microscopic end point of minimum agglutination than carrying out the test on slides with depressions. The end point is the observation with the low power microscope of at least three or four small clumps of not less than three or four cells. This end point must be followed by at least two squares with higher dilutions of agglutinins that are completely negative.)

6. Maximum macroscopic agglutination consisting of one or only several large clumps is called 4 plus. Lesser degrees of agglutination are 3 plus and 2 plus; 1 plus, the smallest amount of agglutination that can be detected, has a finely granular appearance and is the end point. (The next weaker agglutination is read with the low power microscope and recorded as plus minus plus [± +] and consists of many clumps made up of at least half of the cells present. Considerably smaller and fewer clumps are recorded as simply plus minus [±], and minimal clumping, consisting of at least three or four clumps of three to six cells in a low power field, is recorded as plus minus minus [± —], and in the negative tests all of the cells lie free. The end point is very sharp. Except for corroboration, microscope readings are not recommended.)

7. Boerner shaking machine number 3623, A. H. Thomas Company. The machine is made with the rheostat incorporated in the machine and under the shaking platform. The heat from the rheostat dries the tests. Therefore the rheostat should be removed and placed in the circuit some distance away from the shaker.

### TEST TUBE METHOD FOR DETERMINING THE AGGLUTININ TITER

The test is carried out in a series of ¼ by 3 inch test tubes. The same dilutions of plasma are used in this test as in the large slide test.

In each test tube are placed two drops of the appropriate dilution of the plasma and two drops of 1 or 2 per cent suspension of three times washed cells. The tubes are well shaken and allowed to stand at room temperature for two hours or can be centrifuged at low speed for one minute.[8]

After gentle shaking, naked eye readings are made of the agglutination; 4 plus indicates one large clump, 3 plus when several large clumps appear on gentle shaking, 2 plus indicates many smaller clumps and 1 plus when even a few small clumps are seen or the appearance is granular and is the end point.

When microscopic examination is carried out a drop from each tube is removed with a glass rod, placed on the slide, examined under the low power of the microscope and recorded as in the large slide test.

### COMMENT

Of the 1,354 pools, 134 were made of plasma from 50 individual bleedings in each pool, 850 of plasma from 25 bleedings, 355 of plasma from 6 to 10 bleedings, and 15 of plasma from 15 bleedings. The samples of pools containing 15 bleedings had been dried from the frozen state.[9] All other samples were in the original liquid state. Since the plasmas were pooled as they came to each laboratory with no selection of the blood groups of the individual plasmas, the distribution of the blood groups was by chance.

As shown in the table, of the total number of 1,354 pools in our series only 39 pools, or 2.9 per cent, showed a macroscopic anti-A titer of 1:20 or higher, and of these only 3, or 0.2 per cent, a titer of 1:40 or higher (one each 1:40, 1:60 and 1:80), none being higher than 1:80. Eighteen pools, 1.3 per cent, showed an anti-B titer of 1:20 or higher, only one as much as 1:40, and none higher than this. Therefore 97 per cent of the entire series showed both anti-A and anti-B titers less than 1:20 and 99.7 per cent less than 1:40.

From the table it can be seen that the percentage of plasmas falling into these different titration levels, regardless of the number of bleedings constituting each pool, does not show wide variation, with the exception of the group of 15 plasmas each containing 15 bleedings. Here the number examined was small, and the percentages probably cannot be compared statistically with those from the groups with the larger number of samples.

Lozner and Newhouser [3] have recently reported on the anti-A and anti-B isoagglutinin titrations of 1,000 pools of plasma. These were liquid pools containing plasma obtained from 5 to 12 donors. Some of the pools were titrated when they were 1 month old, others 1 to 4 months old, and still others over 4 months old. Our pools were titrated when comparatively fresh, about 1 month old.

They found the titer of the 4 month old pools lower than that of the pools under 4 months. Their total for the entire 1,000 pools, regardless of age, for both anti-A and anti-B agglutinins is 8.9 per cent above the titer of 1:16. Our dilutions were made in multiples of ten, and we found in 1,354 pools a total of

8. The centrifuge technic is useful when saving time is important and is to be highly recommended for cross matching transfusion tests.

9. It has been demonstrated that freezing and drying has little if any effect on agglutinin titer, except possibly to reduce it slightly.

4.2 per cent for both anti-A and anti-B agglutinins, with a titer of 1:20 or higher. Of their pools 3.3 per cent have a titer higher than 1:32, and we found only 0.28 per cent with a titer of 1:40 or higher.

Recently Blum [10] has published the agglutinin titers in forty pools containing liquid plasma from 4 to 7 donors, such as is routine in most hospital blood banks. He used Davidsohn's sensitive technic, with a low power microscope end point, and notes that these titers are higher than those with a macroscopic end point. His titers ranged from less than 1:2 to 1:56, none higher. The averages were 1:9 for anti-A and 1:22 for anti-B. These are even lower than those in Lozner and Newhouser's series.

Even with such a small percentage of pools in our series showing titers higher than 1:40, it seemed important to find out by actual trial if pools with comparatively high titers, definitely higher than the routine pools, could cause any specific reactions or harmful effects when they were administered intravenously to type A or B patients. Consequently the pool which had an anti-A titer of 1:80 was secured, and 500 cc. was administered cautiously by the intravenous route to 10 type A patients. These intravenous injections did not cause any clinical reactions or jaundice in any of the patients.

We then had prepared some pools made up entirely of 25 type O individual plasmas, so that none of the agglutinins would be neutralized and both anti-A and anti-B agglutinins would be the highest that could possibly occur, should a pool by chance be made up entirely of type O plasma. The highest anti-A titer in these pools was 1:256 and the anti-B titer 1:128. The titers of most of the pools varied from 1:8 to 1:64. We were surprised to find the titers this low, expecting higher levels. The most probable explanation is that plasmas with low titers reduced the high titers by dilution. These results give additional confidence that small pools will have a low titer even if all or most of the individual plasmas belong to type O.

These pools yielded about 75 500 cc. units of dried plasma. One third was sent to Capt. L. R. Newhouser (MC), U.S.N., another third to Lieut. Col. D. B. Kendrick, M. C., U. S. Army, and the other third we retained. These pools, when clinical indications arose, were injected intravenously into patients belonging to types A or B.

No patient received less than 500 cc. at one time. One patient received 500 cc. daily for four days and on the fifth day received 1,000 cc.[11] None of these patients showed any reactions, and there were no signs or symptoms of intravascular agglutination or hemolysis. In 6 patients, immediately after the injection, a venous sample was withdrawn from the opposite arm. These samples were collected in citrate solution and examined soon afterward under the microscope. In none were any agglutinates found.

In our series of 1,354 pools of plasma not a single pool was found with an agglutinin titer higher than 1:80. In this series there were 355 pools made up of plasma from only 6 to 10 donors. These pools are the size that are usually prepared in hospitals. We are particularly interested that in this series of small pools there was only 1 pool that had a titer of 1:40, and none higher. Therefore these small pools are just as apt to be free from high agglutinin titers as larger pools made up of from 25 to 50 individual plasmas.

Since full doses of plasma with titers varying from 1:80 to 1:256 were administered intravenously to patients of types A and B and caused no reactions, it seems clear that plasma with titers up to 1:40 certainly cannot cause incompatible reactions, and can be administered safely, regardless of the blood type of the recipient.

## CONCLUSIONS

1. The anti-A and anti-B agglutinin titers were determined in 1,354 pools of human plasma.

2. The number of individual plasmas in the pools varied from 6 to 50.

3. The pools of plasma were either random samples or every fifth or tenth as they were processed routinely.

4. Of the 1,354 plasma pools, only 2 had macroscopic titers of 1:40, 1 of 1:60 and 1 of 1:80. Therefore 99.7 per cent of the pools had macroscopic agglutinin titers, anti-A or anti-B, of less than 1:40. Also in 97 per cent the titer was less than 1:20.

5. In 355 small pools made up of plasma from 6 to 10 individuals, whereas the percentage with relatively low titers, 1:20 to 1:40, was somewhat higher than in pools of a larger number of plasmas, the percentage with titers of 1:40 or higher was not greater than in the larger pools. Therefore it is perfectly safe to prepare small pools of plasma from 6 to 10 donors. The probability of large plasma pools having a high titer is even less than that of small pools.

6. Pools of plasma were prepared entirely of type O plasma so as to secure the highest possible agglutinin titers, both anti-A and anti-B. These titers ranged up to 1:256. Seventy-five 500 cc. dried units of these plasma pools were reconstituted and administered intravenously to type A or B individuals. No reactions were caused, and there were no signs or symptoms of intravascular agglutination from the relatively high titered plasma.

7. Pooled plasma, as prepared in small pools at hospital blood banks or in larger pools at processing laboratories, the blood groups entering each pool by chance and without selection, can be administered with safety to all individuals, regardless of their blood types, and without fear of causing any harm because of isoagglutinin content or of causing any signs or symptoms of intravascular agglutination.

111 East Eightieth Street.

*Macroscopic Readings*

| No. of Plasmas in Each Pool | No. of Samples | Titer 1:20 to 1:39 | | Titer 1:40 | | Titer 1:50 | | Titer 1:60 | | Titer 1:80 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Anti-A | Anti-B | Anti-A | Anti-B | Anti-A | Anti-B | Anti-A | Anti-B | Anti-A | Anti-B |
| 50 | 134 | 2 (1.5%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 25 | 850 | 22 (2.6%) | 7 (0.8%) | 0 | 0 | 0 | 0 | 1 (0.1%) | 0 | 1 (0.1%) | 0 |
| 6-10 | 355 | 11 (3.1%) | 6 (4.5%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | 15 | 1 (6.6%) | 4 (26.4%) | 0 | 1 (6.6%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 1,354 | 36 (2.7%) | 17 (1.25%) | 1 (0.07%) | 1 (0.07%) | | | 1 (0.07%) | | 1 (0.07%) | |

10. Blum, L. L.: Isoagglutinin and Agglutinogen Contents of Pooled Plasma: Their Role in Transfusion Reactions, Am. J. Clin. Path. **14**: 112-118, 1944.

11. Personal communication from Capt. John Elliott, S. C., A. U. S., Surgical Physiology Division, Army Medical School.

# Clinical Notes, Suggestions and New Instruments

## TREATMENT OF HUMAN PSITTACOSIS WITH PENICILLIN

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Previous reports have indicated that penicillin may be of value in the treatment of human psittacosis. Heilman and Herrell [1] demonstrated the protective effect of penicillin on mice experimentally infected with a strain of psittacosis virus of parakeet origin. According to Parker and Diefendorf [2] penicillin has a very definite effect on the course of the disease induced in chick embryos by the virus of psittacosis. Recently penicillin was employed successfully in a human case of ornithosis, which disease is caused by a psittacosis-like virus.[3] Our purpose in this communication is to record a case of human psittacosis in which penicillin seemed to be of definite value.

### REPORT OF CASE

*History.*—E. Q., a white woman aged 52, was referred to the Philadelphia General Hospital Jan. 5, 1945 by her family physician, Dr. Philip Yuckman, because of a pneumonia that did not yield to sulfonamide therapy. Nine days before admission she complained of malaise, generalized body pains, frontal headache and a watery nasal discharge. By the fourth day of illness she had developed a hacking, nonproductive cough, sore throat, fever and frequent nosebleeds. For the next four days she received a total of 12 Gm. of sulfadiazine without improvement and on the ninth day of illness was admitted to the hospital.

*Physical Examination.*—The patient was acutely ill, mentally confused and restless, chiefly because of a rather severe unproductive paroxysmal cough. Her temperature was 104 F., pulse rate 100 and respiratory rate 30. The nose was oozing fresh blood and the pharynx was moderately inflamed. Over the left lower lung posteriorly there was some dulness to percussion and increased breath sounds. At both bases were heard many fine moist inspiratory and expiratory rales. The liver and spleen were not palpable.

*Laboratory Studies.*—The pertinent data pertaining to laboratory and x-ray [4] studies are shown in the accompanying illustrations. A report from Dr. K. F. Meyer [5] stated that a specimen of serum, obtained from the patient on the twenty-third day of illness, fixed complement in presence of psittacosis antigen 1:128 (4 plus). Because other diseases, especially lymphogranuloma venereum,[6] may produce high antibody titers with psittacosis antigen, a Frei test was performed and was negative. Stool and urine cultures as well as routine agglutination tests were all negative. The culture material contained para-aminobenzoic acid and penicillinase. The sputum culture showed a few pneumococci. Differential white blood counts were all normal.

*Clinical Course.*—The septic fever, paroxysmal nonproductive cough, nosebleeds, frontal headache and mental confusion persisted until the twenty-first day of the disease. Repeated chest x-ray examinations revealed a migratory type of pneumonia. Sulfamerazine was given with no effect, and on the nineteenth day of the illness the drug was stopped and penicillin 100,000 units intramuscularly daily was started. Within thirty-six hours of penicillin therapy there was definite clinical improvement. For the first time since admission the patient was clear mentally, the cough became less severe and the nosebleeds subsided. The administration of penicillin was followed also by a definite improvement in the lungs, as revealed by physical and x-ray examinations. Throughout the entire illness the physical chest signs were always less than the x-ray appearance. A relative bradycardia was present most of the time. Recovery was uncomplicated, and the patient is now enjoying apparent good health.

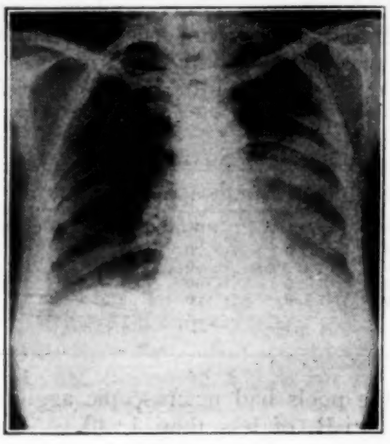

Fig. 1.—Appearance of chest on thirteenth day of disease. Pneumonitis and some pleuritis involving the left lower lobe, with a peculiar irregular bronchopneumonic consolidation. In the right base there is only a small amount of pleural thickening, with early consolidation.

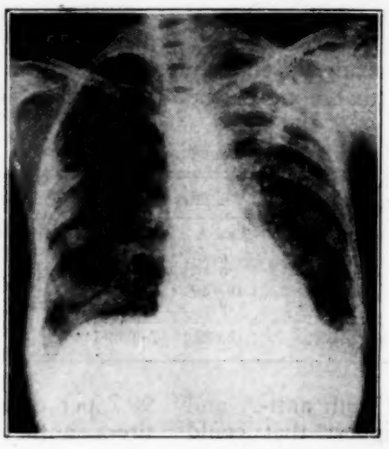

Fig. 2.—Appearance on twentieth day of disease. The left lower lobe now shows much clearing and very little consolidation, but there is now a more recent area of consolidation in the left upper, the lower portion of the right upper and the right lower lobe. There is a peculiar ground glass appearance in the consolidated areas.

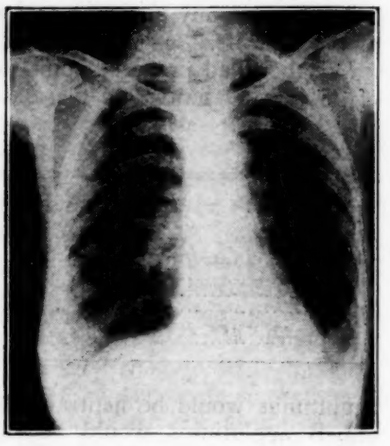

Fig. 3.—Appearance on twenty-seventh day of disease. There is now only a small amount of pleural thickening in the left base. The pneumonic processes have entirely disappeared.

*Epidemiology.*—In late September 1944, about three months before the onset of illness, the patient acquired a parrot. Each day the bird was allowed out of the cage and would fly about the house. On Dec. 20, 1944, seven days before the illness began, the parrot bit the patient on her right middle finger. Aside from this episode there was no other history of contact with parrakeets, love birds, pigeons, doves or chickens.

### SUMMARY AND CONCLUSIONS

The diagnosis of psittacosis in this patient is based on the history of a recent bite by a parrot, a migratory pneumonia which failed to respond to sulfonamides and a significant titer of complement fixing antibodies for psittacosis in the patient's serum. The Frei test was negative and there was no other history of contact with birds or animals which have been

Dr. Gaydosh is David Riesman Fellow in Medicine.
From the Committee on Chemotherapy, Philadelphia General Hospital.
This work was aided by a grant from the Research Fund for Infectious Diseases, University of Pennsylvania.

1. Heilman, F. R., and Herrell, W. E.: Penicillin in the Treatment of Experimental Psittacosis, Proc. Staff Meet., Mayo Clin. **19**: 204 (April 19) 1944.
2. Parker, R. F., and Diefendorf, H. W.: Effect of Penicillin on Certain Viruses, Proc. Soc. Exper. Biol. & Med. **57**: 351 (Dec.) 1944.
3. Turgasen, F. E.: Human Ornithosis Treated with Penicillin, J. A. M. A. **126**: 1150 (Dec. 30) 1944.
4. H. W. Ostrum, chief roentgenologist, Philadelphia General Hospital, Philadelphia.
5. Meyer, K. F., The George Williams Hooper Foundation, University of California, San Francisco.
6. Eaton, M. D.; Martin, W. P., and Beck, M. D.: Antigenic Relationship of Viruses of Meningopneumonitis and Lymphogranuloma Venereum, J. Exper. Med. **75**: 21 (Jan.) 1942.

shown to harbor psittacosis-like viruses. No attempt was made to isolate the virus, and we agree with Meiklejohn and his associates [7] that this is the only satisfactory positive evidence of specific infection. Nevertheless, we believe that this patient represents a case of psittacosis. Penicillin therapy was

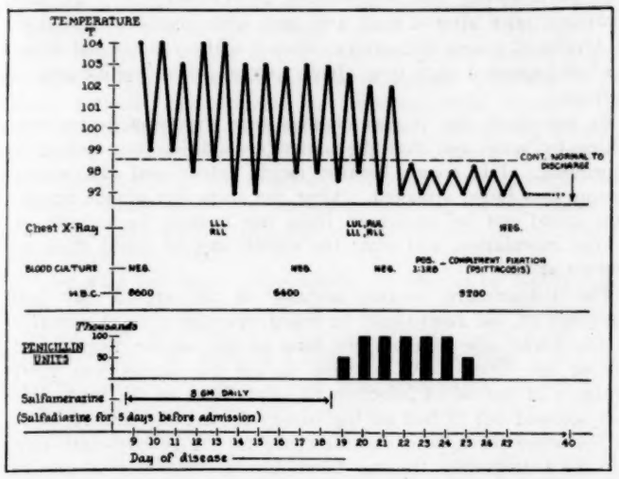


Fig. 4.—Course in case of human psittacosis treated with penicillin.

followed within thirty-six hours by definite clinical improvement. It is our impression that penicillin was of therapeutic value in this case of psittacosis.

255 South Seventeenth Street.

## "DIAPER RASH" DUE TO PERM-ASEPTIC

WILLIAM L. DOBES, M.D., ATLANTA, GA.

In recent months a new antiseptic solution has appeared on the market under the name of Perm-Aseptic-Ramplex. The product is sold as Perm-Aseptic for promotional purposes and as Ramplex for industrial purposes. The product is distributed by the Perm-Aseptic Process Company, New York City. The company advertises the new chemical as a fluid of highly concentrated power which combines the properties of germicide, bactericide and fungicide. According to the company's claims its purpose is to make textiles actively antiseptic as a protection to persons and as a prevention of destruction of textiles by bacteria, germs, mold and mildew.

Bacteriologic tests have been made by Foster D. Snell, Inc., and by the United States Testing Company, Inc. The zone of inhibition is claimed to be 3 to 6 mm. and to conform with the standard for laboratory tests as established by the Food and Drug Administration of the United States government.

Perm-Aseptic is becoming widely used among the diaper services. The diapers are passed through the Perm-Aseptic solution as the last rinse. The recommended dilution varies from 1:10,000 to 1:30,000.

Recently I have seen 5 cases of diaper rash which was caused by Perm-Aseptic. Three of these cases were thoroughly studied and followed.

The age of the infants varied from 2 months to 16 months. The rash appeared as an acute erythema accompanied by a mild edema of the areas involved. In 1 case vesiculation was present. Pruritus was moderate in all cases. The areas involved corresponded to the areas of contact with the diaper. The diapers in all the cases were supplied by a diaper service which in recent months added the Perm-Aseptic to the last rinse.

Three of the cases I had the opportunity to study. The mothers were told to boil the diapers and rinse them out in plain water before using. The diaper rash did not disappear but became less severe in 2 cases and remained the same in the third case. The Perm-Aseptic apparently is not completely removed by boiling and washing. It is claimed that even after several washings Perm-Aseptic is still present in the materials. The mothers were then told to use their own diapers for a few days. Each case rapidly cleared up within three to seven days. When wearing of the diapers from the diaper service was resumed the rash immediately reappeared. This was repeated three times in each case, thus confirming our suspicions that the diapers were the causative agent.

The United States Testing Company, Inc., reported on its patch testing as follows: "Twenty-five samples of cotton fabric previously treated with a 1-400 dilution of Perm-Aseptic Germicide, dried, were placed in contact with human tissue for forty-eight hours, removed for twenty-four hours and then replaced for twenty-four hours. No irritated areas developed on any individual." One of my own cases was patch tested with the diaper, which was passed through a 1:30,000 dilution as the last rinse. The patch test after twenty-four hours was positive.

I have communicated with Dr. Louis Schwartz of the U. S. Public Health Service, Bethesda 14, Md. According to the information received Perm-Aseptic is a primary skin irritant in strong concentration and a sensitizer in weak concentrations. So far cases of contact dermatitis from Perm-Aseptic have not been reported but are likely to occur as this new chemical becomes more widely used. It is evident that one exposure is not as likely to sensitize within three days as numerous exposures over a period of weeks. Each of my patients wore the diapers treated with Perm-Aseptic for at least two months before any symptoms of sensitivity appeared. The diaper service involved was most cooperative and because of the potential dangers the Perm-Aseptic was omitted from the washings. The cases involved have cleared up and no recurrence has been noted in several weeks, although the same diaper service is being used. The fact that the Perm-Aseptic was the only ingredient omitted by the laundry confirms the diagnosis of Perm-Aseptic being the offending agent in the cases of diaper rash described.

478 Peachtree Street.

## PNEUMONIC PLAGUE

### REPORT OF A CASE WITH RECOVERY

EDGAR J. MUNTER, M.D., SAN FRANCISCO
Surgeon (R), United States Public Health Service

Recovery from pneumonic plague is so rare that for all practical purposes the disease is considered fatal. For this reason a case of proved plague pneumonia with recovery is thought to be worthy of recording.

Dr. J. H. was engaged in research investigations at the Plague Investigation Station of the U. S. Public Health Service, San Francisco, and had been so engaged for a period of eighteen months previous to his illness.

During the week before the onset of this illness he had been working with virulent cultures of Pasteurella pestis but had neither inoculated animals nor handled any that had been inoculated, and he had not made any significant changes in his customary bacteriologic technic. On May 31, 1944 he came to the laboratory as usual but returned to his home shortly after his arrival because of the onset of malaise and chilliness, which increased during the day and was accompanied by an occasional hacking cough. On awakening the following morning he found that his temperature was 104 F. and he coughed up some blood tinged sputum. He was promptly brought by automobile from his home and admitted to the U. S. Marine Hospital, San Francisco, at 10 a. m., June 1.

On admission he complained of malaise, slight pain in the chest, low down on the right side, and a frequent nonproductive cough. The patient was aware that he was confused and disoriented. His temperature was 104 F., the pulse rate 100, respiratory rate 26. His throat was slightly injected, but there were no enlarged cervical nodes noted. There was an area of impaired resonance at the base of the right lung posteriorly;

7. Meiklejohn, G.; Beck, M. D., and Eaton, M. D.: Atypical Pneumonia Caused by Psittacosis-like Viruses, J. Clin. Investigation **23**: 167 (March) 1944.

the breath sounds were normal over this area, but there were very fine scattered rales. There was a faint systolic murmur heard at the apex of the heart, but otherwise there seemed to be no cardiac abnormality. The blood pressure was 110/70. The spleen was not palpable. The axillary and inguinal lymph nodes were not enlarged, and the skin of the head, neck, trunk and limbs was clear. The area of impaired resonance over the lung corresponded to a round patch of infiltration, demonstrated by a picture made by a portable x-ray machine (fig. 1).

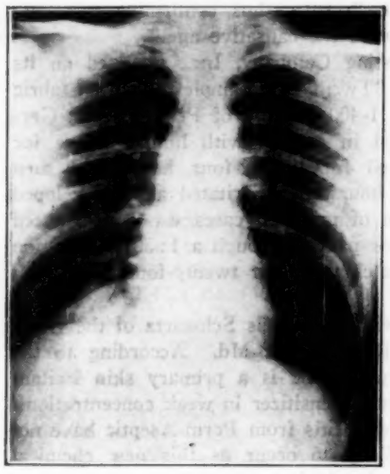

Fig. 1.—Area of consolidation in right lower lobe on entry, June 1.

Blood examination revealed 4,800,000 red blood cells, hemoglobin 13.6 Gm., 18,000 white blood cells, with polymorphonuclears 88 per cent and lymphocytes 12 per cent. The urine was normal. A specimen of approximately 4 cc. of sputum was obtained approximately twenty-four hours after onset through persistent coughing efforts. Examination of the sputum and the bacteriologic, chemical and other laboratory tests were done by the Plague Investigation Station, which is adjacent to the hospital.

The report of Dr. N. E. Wayson, officer in charge of the station, was as follows: "The sputum was very viscid and contained two rather discrete blood tinged portions. A microscopic smear of the blood tinged areas revealed large numbers of bacteria whose morphology and bipolar staining qualities were characteristic of Pasteurella pestis. In some portions of the smear these were the only organisms present and were scattered among leukocytes.

"Cultures of P. pestis were obtained directly from the sputum, checked through differential culture reactions and injected into mice and guinea pigs, which died with the pathologic changes characteristic of plague. Other mice and guinea pigs were inoculated with the sputum in amounts as small as 0.1 cc. by subcutaneous and intracutaneous injections. All died with the pathologic changes characteristic of plague, and pure cultures of P. pestis were obtained from the tissues of several of them. Mice were inoculated with small quantities of the sputum by intraperitoneal injection and their peritoneal contents were examined six to eight hours later for the presence of P. pestis and pneumococci. P. pestis but no pneumococci were found, and the animals were killed twelve and eighteen hours later. Cultures of pestis were obtained from the peritoneal fluid.

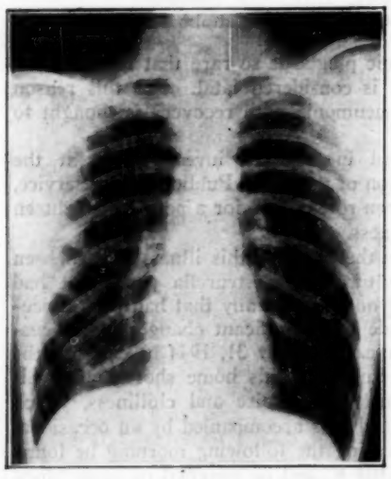

Fig. 2.—Almost complete absorption of lesion forty-one days after onset.

"Ten cc. of blood of the patient was inoculated into Kracke broth, to which para-aminobenzoic acid had been added, and incubated for a period of five days without the appearance of bacterial growth."

The course of the illness was severe and for the first four days the temperature remained between 102.2 and 106.8 F. rectally. Cough was hacking and frequent but not violent, and small amounts of bloody sputum were raised at irregular intervals. During the first six days the patient alternated between periods of delirium and periods of mental clearness, and at times he was so wildly irrational that it required repeated injections of morphine and scopolamine to restrain him. On two occasions, once after a chill and once after maniacal exertion, he developed severe circulatory collapse with cyanosis and dyspnea but improved each time after injections of morphine and of caffeine.

By the sixth day it was obvious that the temperature was falling by lysis, and that the patient's condition was definitely improving. His cough became much milder and the scanty sputum less blood streaked. After the sixth day plague organisms could not be recovered from the sputum by culture or animal inoculation, and after the eighth day he could raise no sputum at all.

The temperature became normal on the eighth day and remained so, but rales could be heard over the area of infection in the lower lobe of the right lung as late as the twenty-first day of the illness. At no time during the illness was there evidence of spread of infection to other lobes of the lung. He was allowed out of bed on the twenty-second day and returned to his home for a long convalescence on the twenty-sixth day. Electrocardiographic tracings taken during convalescence showed no evidence of myocardial damage. X-rays did not show complete clearing of the infiltration in the lung until six weeks had elapsed (fig. 2).

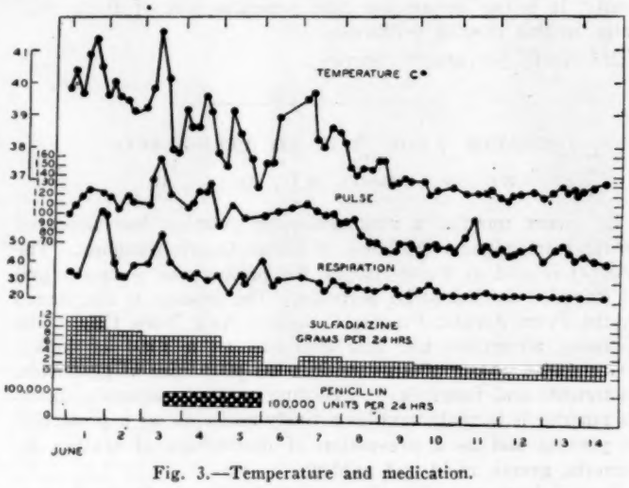


Fig. 3.—Temperature and medication.

Treatment was started immediately with large doses of sulfadiazine, 12 Gm. being given orally in the first twenty hours and 1 Gm. every four hours thereafter. After twenty-four hours the sulfadiazine level was only 4 mg. per hundred cubic centimeters. Two and five-tenths Gm. of sodium sulfadiazine was then given intravenously, and the oral dose was increased to 2 Gm. every six hours. However, the daily blood sulfadiazine level did not rise above 5 mg. per hundred cubic centimeters.

An antiplague rabbit serum was procured from the Hooper Foundation for Medical Research. Small doses of this serum were reported to protect mice against injections of P. pestis.[1] The patient was skin tested with the serum and was found highly sensitive to it and did not respond well to small desensitizing doses. It was believed that his condition was so precarious that a serum reaction might result fatally, and the serum was not used further.

On the fourth day of his illness intramuscular administration of penicillin was started, although it was understood that this drug has not been proved to be effective against infection with plague or other gram negative bacteria. Three hundred thousand units of penicillin was given and there was no evidence that the administration of this drug altered the course of the disease.

1. Meyer, K. F., director, Hooper Foundation for Medical Research: Personal communication to the author.

COMMENT

Primary pneumonic plague is usually fatal and therapeutic methods seem to be fruitless; it is generally attended with the development of secondary cases. However, recovery occasionally occurs [2] and secondary cases do not occur inevitably.

Antiplague serum has been used in the treatment of plague for many years and is reported to have prolonged life in cases of pneumonic plague for several days.[3] There have been a number of reports of the favorable action of sulfonamide drugs in plague,[4] but in practically all instances the reference is to bubonic plague. Sulfathiazole has been repeatedly shown to be more efficacious than sulfapyridine in cases of bubonic plague, and animal experiments have seemed to indicate that sulfadiazine would be superior to either.[5] In the reports of outbreaks of plague which show the apparent lowering of the bubonic plague mortality rate by the sulfonamides the cases of pneumonic plague have been fatal.

As far as I am aware, this case is the first to be reported in which primary pneumonic plague has been treated by the use of sulfadiazine and the patient has recovered. However, the recovery cannot be attributed solely to a favorable action of this drug since other factors may have contributed to it.

The patient had received five injections of plague vaccine over a period of six months, approximately one year previous to his illness. This vaccine had been made from virulent P. pestis organisms which had been chemically killed. Inoculations were made on Jan. 26, 1943, 0.5 cc.; February 2, 1.5 cc.; April 3, 1.0 cc.; April 22, 1.0 cc.; June 11, 1.0 cc. The total amount of vaccine injected contained approximately 122 billion organisms. Shortly after the last injection the administration of the patient's serum to mice afforded them protection against small doses of P. pestis. However, a rather unsatisfactory mouse protection test performed six months later on his serum showed no evidence of protection.

Further, the nature of the illness was recognized within twenty-four hours after its onset and he was afforded treatment with modern facilities very promptly. He was placed in an oxygen tent within an hour after his admission to the hospital, and his specific therapy was started approximately twenty-six hours after he first began to feel ill. He was given every nursing facility, and continued attention was directed toward the protection of his heart against undue damage by sparing him every possible exertion.

Cases of primary pneumonic plague do not invariably give rise to secondary cases even though there is a complete failure to quarantine or segregate contacts.[3] The absence of coughing, sneezing or otherwise infecting the atmosphere with droplets of the patient's sputum have been offered as the probable explanation of the failure of the secondary cases to develop in such instances. This patient had but little cough, but every effort was made to prevent the dissemination of droplets of his sputum in the surrounding atmosphere. It is believed that his treatment in an oxygen tent made an excellent screen between him and his nurses. The attending physician and the nurses were masked, hooded, gowned and gloved and spent the minimum amount of time necessary in the room occupied by the patient. All attendants other than his physician and the nurses assigned to his case were excluded from the three rooms devoted to his care. In order to enter the room occupied by the patient, it was necessary to go into a dressing room and from this through a second room in which all gowns and gloves used in the care of the patient were deposited in a phenol disinfectant previous to returning to the dressing room. As his physician, I carried on with my duties in other parts of the hospital in a somewhat limited manner, but the nurses remained under quarantine.

The manner in which this patient contracted plague is not known to him or to his laboratory associates. There is no evidence to suggest that the pneumonia was secondary to a septicemia following a local infection.

SUMMARY

A case of primary pneumonic plague was contracted accidentally during laboratory research. The nature of the illness was recognized within twenty-six hours after its acute onset, and therapy with sulfadiazine was instituted at once. The patient had received a large amount of plague vaccine a year previous to the illness. He was placed in an oxygen tent promptly on admission to the hospital as a therapeutic and as a quarantine procedure, and other strict quarantine practices were carried out. Secondary cases did not occur.

2. Gale, G. W.: Outbreak of Pneumonic Plague in Kalahari, South African M. J. **15**: 369-373, 1941. Clark, B. M., and Goldberg, S.: Pneumonic Plague: Recovery in a Proved Case, ibid. **17**: 57-60, 1943, and references given in footnote 3.

3. Strong, Richard P., in Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 6, Philadelphia, Blakiston Company, 1942, pp. 660, 661, 695. Wu Lien-Teh: Treatise on Pneumonic Plague, League of Nations' Health Org. Rep., 1926. Report of International Plague Conference, Mukden, 1911, Manila, Bureau of Printing, 1912.

4. Sokhey, S. S.: Annual Report of Haffkine Institute: Studies on Plague, 1939. Girard, G.: Treatment of Plague by Sulfonamides, Bull. Soc. Path. Exot. **34**: 37-48, 1941. Plum, D.: Plague Epidemics in Nairobi, East African M. J. **19**: 3-9, 1942. deVillafane Lastra, Gallardo and Videla: Three Cases of Bubonic Plague Treated with Sulfathiazole, Semana méd. **48**: 1073-1079, 1941. Wagle, P. M.; Sokhey, S. S.; Dikshit, B. B., and Ganapathi, K.: Chemotherapy in Plague, Indian M. Gaz. **76**: 29-32, 1941. Sokhey, S. S., and Dikshit, B. B.: Sulfathiazole in Bubonic Plague, Lancet **1**: 1040-1042, 1940. deVillafane Lastra, Goobar, Rodeiro and Videla: Treatment of Plague, Primer Congr. Nac. Enfermedades, Endemo-epidemicas, Buenos Aires, No. 9, pp. 586-593, 1942. Cassio, Pedro: Plague in Argentina, Bol. Sanitario, Buenos Aires **6**: 167-168, 1941. Sokhey, S. S., and Wagle, P. M.: Report of Haffkine Institute for 1940 and 1941, pp. 37-45.

5. Wayson, N. E., and McMahon, M. D.: Plague: Sulfadiazine Treatment of Guinea Pigs Infected by Artificial Methods, Pub. Health Rep. **59**: 385-397, 1944. Girard.[4] Wagle, Sokhey, Dikshit and Ganapathi.[4] Sokhey and Dikshit.[4] deVillafane Lastra, Goobar, Rodeiro and Videla.[4] Sokhey and Wagle.[4]

## Council on Foods and Nutrition

### SPECIAL ARTICLE

*This is the fifth of a series of articles discussing the significance of protein nutrition in health and disease. This material was prepared by the authors at the request of the Council and has been authorized for publication.*

GEORGE K. ANDERSON, M.D., *Secretary.*

## PROTEIN NUTRITION IN PEDIATRICS

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NEW YORK

In addition to the many functions subserved by protein in adults, this foodstuff serves the special function in the child of providing basic building materials for the manufacture of tissues during growth. Protein also acts by virtue of its chemical and physiologic properties as a therapeutic agent in certain ailments peculiar to infancy and childhood; less commonly it may be biologically harmful when administered to children in its native state.

### PROTEIN NEEDS FOR GROWTH

Protein needs for human growth are both qualitative and quantitative. Knowledge of these needs stems from studies on animals (notably the young white rat) and human observations including dietary surveys, measurements of nitrogen balance and creatinine excretion in urine and estimations of the rate and composition of growth at varying levels of protein intake and at different ages. Dietary prescription to meet these needs depends on such dietary factors as the biologic value of the proteins (amino acid mixture) ingested, their coefficients of digestibility, the degree of preparatory heating, the caloric, vitamin and mineral intake, sulfonamide medication [1] and such physiologic factors as pregnancy, puberty, the menarche, lactation, the state of nutrition and health, and age. Besides these known

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

1. Martin, G. J.: Mixtures of Pure Amino Acids as Substitutes for Dietary Protein, Proc. Soc. Exper. Biol. & Med. **55**: 182 (March) 1944.

conditioning factors, other issues of a more controversial nature preclude complete acceptance of currently established protein quotas for human growth: (*a*) the questionable validity of transposing to infants and children experimental data and conclusions derived from young animals and human adults;[2] (*b*) lack of acceptable clinical criteria for defining optimal as against average and maximal nutrition and protein requirements; (*c*) a paucity of quantitative information of the composition of essential amino acid mixtures conducive to optimal human growth.[3]

In the present state of knowledge an adequate protein intake for the infant and child may be defined as one which contains all the known essential (and perhaps nonessential) amino acids in sufficient amounts and in palatable and digestible form to cover maintenance needs and to provide in addition the surplus for protein deposition within the body compatible with normal growth.

*Qualitative Considerations.*—Proof is convincing that the young white rat grows in normal fashion when the sole source of dietary protein consists of a mixture of the following ten highly purified amino acids: arginine,[4] histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine.[5] Applicability of these results to other animals and to human beings is suggested by recent observations on the nitrogen balance of dogs,[6] infants [7] and adults [8] and on the manufacture of hemoglobin and serum proteins by animals and man [9] receiving natural proteins, amino acid mixtures as such or as casein hydrolysates. The nitrogen studies showed that positive nitrogen balances of similar magnitude resulted on equivalent intakes, irrespective of the source of dietary nitrogen. Pending long term observations of growth curves and physical fitness of infants and children receiving pure mixtures of essential amino acids, final proof is lacking that the rest of the protein molecule and its fourteen or more constituent amino acids are of no nutritional importance.[10] Furthermore, quantitative data on the relative importance of each of the essential amino acids are still sparse. The absolute amounts and percentage composition of amino acid mixtures conducive to optimal human growth are not yet known. Reliance for growth and maintenance of health remains with the natural protein foodstuffs; use of purified amino acid mixtures and casein hydrolysates is for the present reserved for the treatment of abnormal states in which the ingestion or assimilation of natural proteins is difficult or detrimental.[11]

TABLE 1.—*Percentage Amino Acid Composition of Proteins in Some Foods Commonly Used by Infants and Children* *

| | Milk † | | | | |
|---|---|---|---|---|---|
| | Lactalbumin | Casein | Egg | Meat | White Bread |
| Nitrogen | 16.0 | 16.0 | 16.0 | 16.0 | 16.0 |
| Arginine | 3.5 | 4.1 | 7.0 | 7.2 | 3.5 |
| Histidine | 2.0 | 2.5 | 2.4 | 2.1 | 2.3 |
| Isoleucine | 4.5 | 6.5 | 5.3 | 3.4 | 2.8 |
| Leucine | 12.2 | 12.1 | 19.0 | 12.1 | 11.2 |
| Lysine | 8.0 | 6.9 | 6.0 | 7.6 | 2.8 |
| Methionine | 2.8 | 3.5 | 3.5 | 3.3§ | 2.3 |
| Phenylalanine | 5.6 | 5.2 | 5.2 | 4.5 | 5.1 |
| Threonine | 5.3 | 3.9 | 4.9 | 5.3 | 2.8 |
| Tryptophan | 2.3 | 1.8 | 1.1 | 1.2 | 1.3 |
| Valine | 4.0 | 7.0 | 4.4 | 3.4 | 3.1 |

All values determined on a basis of 16 per cent nitrogen.

* Block, R. J., and Bolling, D.: The Amino Acid Composition of Proteins and Foods, Springfield, Ill., C. C Thomas, Publisher, 1945.

† The protein content of human milk averages 1.25 per cent (0.2 per cent nitrogen), the casein fraction comprising 0.50 per cent and the whey proteins (chiefly lactalbumin), 0.75 per cent. Corresponding values for cow's milk are 3.5 per cent protein (0.56 per cent nitrogen), 2.8 per cent casein, and 0.7 per cent whey proteins.

§ Stare, F. J., and Hegsted, D. M.: The Nutritive Value of Wheat Germ, Corn Germ and Oat Proteins, Federation Proc. **3**: 120 (June) 1944.

Fortunately, from the practical standpoint of feeding infants and children, the protein foodstuffs of animal origin in common usage (milk and milk products, meat, fish, eggs) supply all of the essential amino acids, and some of vegetable origin (whole grain cereals, bread, potato, legumes) supply most of them in varying but generally high concentrations.

*Quantitative Considerations.*—The quantity as well as the quality of dietary protein must be adequate to cover (*a*) maintenance needs [12]—the replacement or wear and tear quota and fecal loss—and (*b*) the growth quota. The wear and tear quota is a measure of metabolized protein. It varies with the caloric and protein intake and with the energy expenditure of the subject. It is estimated by analysis of the urinary nitrogen ($\times$ 6.25). The fecal loss is a measure of the coefficient of digestibility of ingested protein and it is determined by similar analysis of the stools. In the absence of diarrhea and with the types and amounts of protein foods commonly used by infants and children, fecal loss of protein averages 10 per cent of the intake at all ages. The difference between the intake and the combined excretion in urine and feces or the magnitude of the nitrogen balance ($\times$ 6.25) affords an estimate of the protein deposited in the body for physical growth and pre-

2. Kinsey, V. E., and Grant, W. M.: Adequacy of the Essential Amino Acids for Growth of the Rat, Science **99**: 303 (April 14) 1944. Almquist, H. J.: The Amino Acid Requirements and Protein Metabolism of the Avian Organism, Federation Proc. **1**: 269 (Sept.) 1942. Rose, W. C.; Hanes, W. J.; Johnson, J. E., and Warner, D. T.: Further Experiments on the Role of the Amino Acids in Human Nutrition, J. Biol. Chem. **148**: 457 (May) 1943. Holt, L. E., Jr.; Albanese, A. A.; Shettles, L. B.: Kadji, C., and Wangerin, D. M.: Studies of Experimental Amino Acid Deficiency in Man: I. Nitrogen Balance, Federation Proc. **1** (Pt. 2): 116 (March 16) 1942.

3. Hier, S. W.; Graham, C. E., and Klein, D.: Inhibitory Effect of Certain Amino Acids on Growth of Young Male Rats, Proc. Soc. Exper. Biol. & Med. **56**: 187 (June) 1944. White, A., and Sayers, M. A.: Accelerated Rat Growth Rate on Dietary Nitrogen Obtained from Pancreas, ibid. **51**: 270 (Nov.) 1942.

4. Arginine is synthesized by the animal organism but not at a rate rapid enough to meet the demands for normal growth.

5. Rose, W. C.: The Nutritive Significance of Amino Acids, Physiol. Rev. **18**: 109 (Jan.) 1938. Rose, W. C., and Fierke, S. S.: The Relation of Aspartic Acid and Glucosamine to Growth, J. Biol. Chem. **143**: 115 (March) 1942.

6. Rose, W. C., and Rice, E. E.: The Significance of the Amino Acids in Canine Nutrition, Science **90**: 186 (Aug. 25) 1939.

7. Hartmann, A. F.; Meeker, C. S.; Perley, A. M., and McGinnis, H. G.: Studies of Amino Acid Administration; Utilization of Enzymatic Digest of Casein, J. Pediat. **20**: 308 (March) 1942. Shohl, A. T.; Butler, A. M.; Blackfan, K. D., and MacLachlan, E.: Nitrogen Metabolism During the Oral and Parenteral Administration of the Amino Acids of Hydrolyzed Casein, ibid. **15**: 469 (Oct.) 1939.

8. Albanese, A. A.; Holt, L. E., Jr.; Brumback, J. E., Jr.; Kadji, C., and Wangerin, D. M.: Nitrogen Balance in Experimental Lysine Deficiency in Man, Proc. Soc. Exper. Biol. & Med. **48**: 728 (Dec.) 1941. Holt, L. E., Jr.; Albanese, A. A.; Brumback, J. E., Jr.; Kadji, C., and Wangerin, D.: Nitrogen Balance in Experimental Tryptophan Deficiency in Man, ibid. **48**: 726 (Dec.) 1941. Rose, Hanes, Johnson and Warner.[2]

9. Beiling, C. A., and Lee, R. E.: Treatment of Hypoproteinemia by Oral Administration of Protein Hydrolysates, Arch. Surg. **43**: 735 (Nov.) 1941. Robscheit-Robbins, Frieda S.; Miller, L. L., and Whipple, G. H.: Hemoglobin and Plasma Protein: Simultaneous Production During Continued Bleeding as Influenced by Amino Acids, Plasma, Hemoglobin and Digests of Serum, Hemoglobin and Casein, J. Exper. Med. **77**: 375 (April) 1943. Madden, S. C.; Carter, J. R.; Kattus, A. A., Jr.; Miller, L. L., and Whipple, G. H.: Ten Amino Acids Essential for Plasma Protein Production Effective Orally or Intravenously, ibid. **77**: 277 (March) 1943. Elman, R., and Lischer, C.: The Occurrence and Correction of Hypoproteinemia (Hypoalbuminemia) in Surgical Patients, Surg., Gynec. & Obst. **76**: 503 (June) 1943.

10. Lewis, H. B.: Proteins in Nutrition, J. A. M. A. **120**: 198 (Sept. 19) 1942. Albanese, A. A., and Irby, V.: Observations on the Biological Value of a Mixture of Essential Amino Acids, Science **98**: 286 Sept. 24) 1943. Bauer, C. D., and Berg, C. P.: The Amino Acids Required for Growth in Mice and the Availability of Their Optical Isomers, J. Nutrition **26**: 51 (July) 1943.

11. Elman, R.: Parenteral Replacement of Protein with the Amino Acids of Hydrolyzed Casein, Ann. Surg. **112**: 594 (Oct.) 1940. Farr, L. E.: Indications for the Therapeutic Use of Intravenous Amino Acids, Connecticut M. J. **5**: 24 (Jan.) 1941.

12. The specific dynamic action of protein is a by-product and not an intrinsic maintenance need for this foodstuff. On the usual milk diets of infants and mixed diets of children this effect produces a rise of between 5 and 10 per cent above basal metabolic levels. Similarly, exercise does not raise the protein requirement, provided the total dietary calories are adequate.

sumably for other anabolic functions such as the manufacture of serum proteins and formation of enzymes, hormones and antibodies above antecedent levels.

Besides measurements of nitrogen balance, adequacy of the protein intake for growth is also judged by the rate and composition of gain in body weight. The latter may be estimated from the creatinine output in the urine and from the ratio of nitrogen retained to total accretion of body weight. A total gain of body weight conforming to the normal growth curve for height and age as estimated from standard weight tables, with the concurrent deposition of protein per unit of weight gain in amounts approximating the nitrogen content of the body as chemically determined (from 2.0 per cent in the newborn to 2.6 per cent in adults),[13] presumably characterizes an optimal state of quantitative and qualitative growth and nutrition.

Based on such evidence, the Food and Nutrition Board of the National Research Council has recently proposed daily allowances which may be accepted as an approximate guide of the protein requirements during growth. For physicians having a special interest in children, these allowances will serve a more useful purpose if they are amplified to include premature infants and broken down into shorter age intervals for the infantile period.

Provided the dietary protein is chiefly of animal origin and in digestible form and the regimen is adequate in all the other known nutrients, these allowances afford a good margin of safety for healthy infants and children. If a child does not thrive on this regimen the fault probably rests with him, his parents or the environment and not with the diet per se. On the other hand, it should be stressed that all dietary regimens are subject to modification. A diet should conform to the needs of the individual child and not the child to the diet.

TABLE 2.—*Recommended Daily Allowances for Protein, Expanded for the Growing Period*

| Subject | Age | Protein in Grams * Total 1 | Per Kg. 2 | Per Lb. 3 | % of Dietary Calories Average |
|---|---|---|---|---|---|
| Premature † | 1 week to 1 month | | 6.0-4.4 | 2.7-2.0 | 17 |
| Premature ‡ | 1 week to 1 month | 4-3 | 5.0-4.4 | 2.3-2.0 | 15 |
| Premature | 1 to 3 months | per | 4.4-3.3 | 2.0-1.5 | 13 |
| Full term | 2 days to 3 months | Kg. | 4.4-3.3 | 2.0-1.5 | 13 |
| All infants | 4 months to 1 year | | 4.0-3.0 | 1.8-1.4 | 13 |
| Toddlers | 1 through 3 years | 40 | (4.2-2.9) | (1.9-1.3) | (13) |
| Preschool | 4 through 6 years | 50 | (3.3-2.5) | (1.5-1.1) | (13) |
| School | 7 through 9 years | 60 | (2.6-2.1) | (1.2-1.0) | (12) |
| School | 10 through 12 years | 70 | (2.2-1.8) | (1.0-0.8) | (11) |
| Youths, female | 13 through 15 years | 80 | (1.8-1.5) | (0.8-0.7) | (11) |
| Youths, male | 13 through 15 years | 85 | (2.0-1.7) | (0.9-0.8) | (11) |
| Youths, female | 16 through 20 years | 75 | (1.6-1.4) | (0.7-0.6) | (13) |
| Youths, male | 16 through 20 years | 100 | (2.1-1.7) | (1.0-0.8) | (11) |

* Column 1 gives the allowances recommended by the Food and Nutrition Board, columns 2 and 3 the suggested modifications for infants. The figures in parentheses in these columns, beyond 1 year, represent the total allowances in the original recommendations (column 1) per unit of body weight on the basis of average weights for age groups derived from the tables of Baldwin and Wood.
† Premature infants weighing less than 2,000 Gm. (4 pounds 6 ounces).
‡ Premature infants weighing 2,000 Gm. and over.

The high level of protein intake advocated for young premature infants calls for an explanation. Many of these infants have difficulty in digesting and absorbing fat.[14] Their dietary calories are therefore preferentially derived from protein and carbohydrate. Human milk, when fed in the amounts needed to meet the high requirements for maintenance and growth (120 calories per kilogram, 55 per pound), furnishes, per kilogram of body weight, 180 cc. of fluid (2.7 ounces per pound), 2.2 Gm. of protein (1 Gm. per pound), 6.7 Gm. of fat (3 Gm. per pound) and 13 Gm. of carbohydrate (6 Gm. per pound). Although this level of dietary protein in the form of human milk is compatible with

TABLE 3.—*Formulas for Feeding Premature Infants per Kilogram of Body Weight and in Percentages of Dietary Calories*

| Milk | | | | Protein | | Fat | | Carbohydrate | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Type | Amount, Cc. | Sugar, Gm. | Water, Cc. | Gm. | Per Cent | Gm. | Per Cent | Gm. | Per Cent | Calories |
| Human..... | 180 | .. | 0 | 2.2 | 7 | 6.7 | 50 | 12.9 | 43 | 120 |
| Cow's | | | | | | | | | | |
| Whole | 100 | 13 | 50 | 3.5 | 13 | 3.5 | 27 | 17.8 | 60 | 120 |
| Lactic acid | 140 | 6 | .. | 4.8 | 16 | 5.5 | 41 | 12.9 | 43 | 120 |
| Evaporated | 70 | 6 | 80 | 4.8 | 16 | 5.5 | 41 | 12.9 | 43 | 120 |
| Powdered half skimmed (Alacta) | 18 | 11 | 150 | 6.0 | 20 | 2.2 | 16 | 19.4 | 64 | 120 |

positive nitrogen balances of appreciable magnitude (between 0.2 and 0.25 Gm. per kilogram) the total fluid intake is excessive and the level of dietary fat frequently exceeds the fat tolerance of these subjects, especially of those weighing 1,500 Gm. (3 pounds 6 ounces) or less. For these and other reasons [15] heated cow's milk mixtures are preferred in the routine feeding of small and young premature infants.

In isocaloric amounts (120 calories per kilogram) cow's milk mixtures may be prepared to provide less total fluid and fat, higher protein, and equivalent or higher carbohydrate. Examples of such mixtures are given in table 3. Comparative studies of such mixtures of heated cow's milk and of unmodified human milk for the past ten years in the premature unit of the New York Hospital [16] favor the former feedings. The daily gain in total body weight is more constant and at higher levels (25 to 30 Gm. as against perhaps 15 to 20 Gm.), the nitrogen balances are of higher magnitude (0.3 Gm. or more per kilogram as against 0.25 Gm. or less) and the coefficient of digestibility of the more liberal protein intakes is not reduced (85 to 90 per cent at all levels of dietary protein). It may further be pointed out that intakes of human and heated cow's milk of equivalent but lower protein content (2 to 3 Gm. per kilogram) yield absolute and percentile retentions of nitrogen of similar magnitude (0.2 + Gm. per kilogram and above 50 per cent of the intake [17]). This parity of utilization above maintenance levels of the proteins of human and cow's milk for growth in premature infants, contrary to the findings in animals,[18] is in accord with expectation on the basis of the qualitative similarity of amino acid composition of the milk proteins, casein and lactalbumin, noted in table 1. For

13. Vierordt, H.: Anatomische, physiologische und physikalische Daten und Habellen, Jena, G. Fischer, 1906.
14. Gordon, H. H., and McNamara, H.: Fat Excretion of Premature Infants: I. Effect on Fecal Fat Decreasing Fat Intake, Am. J. Dis. Child. **62**: 328 (Aug.) 1941.
15. Catherwood, R., and Stearns, G.: Creatine and Creatinine Excretion in Infancy, J. Biol. Chem. **119**: 201 (June) 1937. Benjamin, H. R.; Gordon, H. H., and Marples, E.: Calcium and Phosphorus Requirements of Premature Infants, Am. J. Dis. Child. **65**: 412 (March) 1943.
16. These studies have been carried out by Dr. H. H. Gordon with the aid of the Children's Bureau of the United States Department of Labor. The results have not yet been fully analyzed and tabulated.
17. Gordon, H. H.; Levine, S. Z.; Wheatley, M. A., and Marples, E.: Respiratory Metabolism in Infancy and in Childhood: XX. The Nitrogen Metabolism in Premature Infants—Comparative Studies of Human Milk and Cow's Milk, Am. J. Dis. Child. **54**: 1030 (Nov.) 1937.
18. Kik, M. C.: Nutritive Value of Lactalbumin versus Casein, Proc. Soc. Exper. Biol. & Med. **37**: 129 (Oct.) 1937.

heavier and older premature infants, better able to tolerate fat and high fluid intakes, human milk is as satisfactory as cow's milk mixtures of higher protein content.

As the absolute rate of growth decelerates in later infancy, the protein intake may be correspondingly reduced to the recommended daily levels of 3 to 4 Gm. per kilogram of body weight. Concomitant with this decline in total increment of daily weight gain, the absolute and percentile retentions of dietary protein at equivalent and adequate intakes has been found to decline from average levels of 0.3 Gm. of nitrogen per kilogram or above 50 per cent of the intake in premature infants and of 0.2 Gm. or less than 40 per cent in full term infants under 3 months of age to average levels of 0.15 Gm. or 15 per cent for infants 5 months of age and older.[19] Analysis of available data for infants under 1 year establishes that the recommended daily allowances of protein as modified in table 2 are compatible with a normal rate of total weight gain and a ratio of nitrogen retained to total increment of gain which approximates the rising nitrogen content of the body (from 2.0 per cent at birth to more than 2.5 per cent during the growing period[20]).

Protein intakes below 2.2 Gm. per kilogram (1 Gm. per pound) in infancy may lead to negative nitrogen balances; levels above those recommended are wasteful since there are no body depots for reserve protein, absorbed amino acids in excess of the needs for growth and maintenance entering interchangeably with fat and carbohydrate into the energy exchange; excess of dietary protein may tax the kidneys by increased excretion of nitrogenous end products, and some of the incoming amino acids may be incompletely metabolized by the young infant in the absence of added vitamins.[21]

With further deceleration in the growth curve with increasing age beyond infancy, lower levels of dietary protein per unit of body weight are required for nitrogen retention and protein deposition. The daily allowances recommended by the National Research Council are generally acceptable. Based on average weights for each group, these allowances progressively fall from a maximal level of 4 Gm. per kilogram at 1 year of age to 1.4 Gm. per kilogram for girls of 20 years. The percentage of dietary calories (at the recommended levels) derived from protein remains constant between 11 and 13 per cent for all ages. The bulk of available evidence indicates that the recommendations are compatible with normal qualitative and quantitative nutrition as judged by dietary surveys, nitrogen balance studies, urinary excretion of creatinine, growth curves and clinical appraisement.[22] Some observers report improvement in measurements of children of preschool and school age on higher protein intakes of 4 Gm. as against 3 Gm. per kilogram.[23] Whether such acceleration is desirable raises the perennial question of maximal versus optimal nutrition, a problem which awaits further study and clarification. It seems valid to state that in the presence of undernutrition from any cause the higher allowances are preferable.[24]

*Dietary Prescription.*—Human or cow's milk ordinarily comprises the sole protein-containing food in early infancy. The protein content of human milk averages 1.25 per cent (0.75 per cent whey proteins, 0.50 per cent casein), that of cow's milk, 3.5 per cent (0.7 per cent whey proteins, 2.8 per cent casein). Since both casein and the whey proteins of milk contain abundant and comparable amounts (per gram of protein) of all the amino acids (except leucine) essential for growth in young animals and presumably in infants (table 1), the protein needs for growth are automatically met by providing sufficient milk. The concept of a higher biologic value of human over cow's milk, erroneously postulated on the basis of a deficiency of cystine in the casein fraction, has been discarded since it has been shown[25] that methionine and not cystine is the sulfur-containing amino acid required for growth and that cow's milk contains the latter amino acid in concentrations as high as or higher than human milk. From the standpoint of protein alone, it seems fair to conclude on the basis of current information that in equivalent content of protein above maintenance levels the two milks are equally nutritious.

A daily allowance (from the first few days after birth) of 175 to 200 cc. of human milk per kilogram of body weight (2½ to 3 ounces per pound) or of 100 to 130 cc. of heated cow's milk (1½ to 2 ounces per pound) covers the protein needs of young full term infants. The daily allowance of cow's milk for young premature infants, as previously indicated, is better set at somewhat higher levels (130 to 140 cc. per kilogram). For older infants in both groups the lower levels are adequate.

When the infant is old enough to take additional foods, other proteins of animal origin (eggs, meat, cheese, fish) and some vegetable proteins (cereals, bread, potato, legumes) progressively replace milk as the sole source of protein. It is a good rule to limit the daily intake of milk in the infantile period to a maximum of 1 liter (quart) and to introduce solid foods in the diet at around 4 months. In children above infancy, from two thirds to three fourths of the total protein intake is preferably derived from animal sources, approximately 50 per cent of total dietary protein being supplied by milk (750 cc. or 1½ pints), 25 per cent by meat and eggs, 15 per cent by bread, cereals and potato, and the remaining 10 per cent by fruits, vegetables and other foods.[26] Dietary surveys reveal that the amounts and distribution of protein in the daily diets of growing children are below the

19. Levine, S. Z.; McEachern, T. H.; Wheatley, M. A.; Marples, E., and Kelly, M. D.: Respiratory Metabolism in Infancy and in Childhood: XV. Daily Energy Requirements of Normal Infants, Am. J. Dis. Child. **50**: 596 (Sept.) 1935. Marples, E.: Creatinuria in Infancy and in Childhood: II. Creatinuria of Premature Infants, ibid. **64**: 996 (Dec.) 1942. Gordon, Levine, Wheatley and Marples.[17] Gordon and McNamara.[14]

20. Stearns, G.: The Mineral Metabolism of Normal Infants, Physiol. Rev. **19**: 415 (July) 1939. Moulton, C. R.: Age and Chemical Development in Mammals, J. Biol. Chem. **57**: 79 (Aug.) 1923.

21. Levine, S. Z.; Dann, M., and Marples, E.: A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants: III. Demonstration of the Irreversible Conversion of Phenylalanine to Tyrosine in the Human Organism, J. Clin. Investigation **22**: 551 (July) 1943; and earlier papers of series.

22. Koehne, M., and Morrell, E.: Food Requirement of Girls from 6 to 13 Years of Age, Am. J. Dis. Child. **47**: 548 (March) 1934. Wait, B., and Roberts, L. J.: Studies in the Food Requirement of Adolescent Girls: III. The Protein Intake of Well Nourished Girls 10 to 16 Years of Age, J. Am. Dietet. A. **8**: 403 (Jan.) 1933. Rose, M. S.: The Foundations of Nutrition, New York, Macmillan Company, 1933. Daniels, A. L.; Hutton, M. K.; Knott, E. M.; Wright, O. E.; Everson, G. J., and Schoular, F.: A Study of the Protein Needs of Preschool Children, J. Nutrition **9**: 91 (Jan.) 1935. Maroney, J. W., and Johnstone, J. A.: Caloric and Protein Requirements and Basal Metabolism of Children from 4 to 14 Years, Am. J. Dis. Child. **54**: 29 (July) 1937.

23. Hawks, J. E.; Bray, M. M., and Dye, M.: The Influence of Diet on the Nitrogen Balances of Preschool Children, J. Nutrition **15**: 125 (Feb.) 1938.

24. Wang, C. C.; Kern, R., and Kaucher, M.: Metabolism of Undernourished Children: IX. A Study of the Basal Metabolism, Caloric Balance and Protein Metabolism During a Period of Gain in Weight, Am. J. Dis. Child. **38**: 476 (Sept.) 1929.

25. Rose, W. C., and Wood, T. R.: The Synthesis of Cystine in Vivo, J. Biol. Chem. **141**: 381 (Nov.) 1941. Womack, M.; Kemmerer, K. S., and Rose, W. C.: The Relation of Cystine and Methionine to Growth, ibid. **121**: 403 (Nov.) 1937.

26. Butler, A. M.: Nutritional Requirements in Infancy and in Childhood, Am. J. Dis. Child. **64**: 898 (Nov.) 1942. Boyd, J. D.: Prescribed Diets for Normal Children, J. Pediat. **24**: 616 (June) 1944.

recommended levels in many parts of the country.[27] The quantities and sources of proteins in the common foodstuffs are reviewed in another paper of this series.[28]

## PROTEINS IN DISEASE

The role of proteins and their constituent amino acids for growth in health is likewise important in such abnormal states as malnutrition, obesity treated by reduction diets, epilepsy treated by ketogenic diets, diabetes mellitus, recovery from acute illness and in the course of chronic disease. Fever, starvation and malnutrition further deplete the already meager stores of body protein, which are of lower magnitude to begin with in children than in adults and in those whose rate of metabolism is higher. The heightened needs in these conditions require attention in planning dietary regimens.

Besides this generally increased demand for protein in illness, this foodstuff by virtue of its unique properties serves a specific role as a therapeutic agent in certain states. The roles of protein and amino acid therapy in pregnancy, lactation and disease are reviewed in other papers of this series.[29] This section presents a brief outline of the use of protein in some disorders common to infants and children.

*Disorders of the Alimentary Tract.*—In health the coefficient of digestibility of protein is high, only 10 per cent or so of the intake being lost in feces. This high tolerance for protein is least impaired of all the organic foodstuffs in most digestive disturbances of infants and children. This fact, doubtless ascribable to the high levels even in early infancy of gastric rennin and pepsin, pancreatic trypsin and chymotrypsin and intestinal peptidases, explains the usage of properly heated milk mixtures, relatively high in protein and low in fat and carbohydrate, as the common method of resumption of enteral feeding in the recovery period of epidemic diarrhea of the newborn and infantile diarrhea of enteral and parenteral origin. Such mixtures include protein milk, skimmed lactic acid milk and skimmed milk with or without added casein. For analogous reasons, diets of high protein content form the basis of regimens in such specific disturbances of the alimentary tract as pancreatic fibrosis, the celiac syndrome (chronic intestinal indigestion) and ulcerative colitis, in the absence of an allergic basis for the two latter conditions.

Since ample evidence is at hand to show that the minimal amounts of unaltered protein normally absorbed into the blood stream are increased in digestive disturbances in early life,[30] predigested proteins in the form of enzymatic casein hydrolysates are gradually replacing native proteins in treatment during the acute stage of many of these conditions.[31] This form of therapy has the advantage of minimizing the hazard of subsequent hypersensitiveness.

*Conditions Associated with Edema.*—The importance and explanation of action of the blood serum proteins in regulating oncotic pressure relationships and fluid balance in the body are well known. They rise normally from average levels of 5.5 Gm. per hundred cubic centimeters at birth (albumin 3.8 per cent, globulin 1.7 per cent) to 7.0 Gm. per hundred cubic centimeters (albumin 5.0 per cent, globulin 2.0 per cent) at 2 years. The specific property of the serum proteins, particularly the albumin fraction, of combating edema forms the basis for the abundant administration of this foodstuff in such conditions of infancy and childhood as nutritional edema, infectious colitis, lipoid nephrosis, extensive burns, other states inducing shock, and juvenile cirrhosis of the liver. The hypoproteinemia common to all these conditions is explained in the 6 instances respectively by inadequate intake, excess fecal loss, excessive urinary excretion, skin seepage, plasmapheresis or hemorrhage, and defective production within the body. Natural proteins by mouth, enzymatic casein hydrolysates enterally and parenterally, whole blood, plasma and serum transfusions have been used with varying effect. The reader is referred to the other papers of this series and to other articles[32] which review the relative efficacy and the amounts of these substances recommended for therapy.

*Allergic States.*—Food allergies are more common in infants and young children than in later life. This predilection is probably explained by the greater permeability of the intestinal tract of these subjects to unaltered protein.[33] The most commonly implicated protein foods are milk, egg, meat, fish and wheat. In order of increasing age, clinical sensitivity to protein is manifested by infantile eczema, angioneurotic edema, mucous colitis and bronchial asthma. Detection of the responsible protein or proteins is made preferably by therapeutic test (ingestion) or by skin tests. If possible, avoidance of the specific foodstuff with the substitution of other protein foods is the therapeutic method of choice. If this cannot be done, immunization (desensitization) may be attempted. Because of the biologic nonspecificity of amino acids, such mixtures, as they become more readily available, will undoubtedly serve an increasingly important therapeutic role in these conditions.[34]

An attempt has been made in this brief review to evaluate the specific role of protein in pediatrics. It should be emphasized, in closing, that many conditioning factors, both dietary and physiologic, influence the requirements for this foodstuff, and that they must be given consideration in the dietary prescription of protein for infants and children in health and in disease.

525 East Sixty-Eighth Street.

27. Inadequate Diets and Nutritional Deficiencies in the United States: Their Prevalence and Significance, Bulletin 109, National Research Council, November 1943.

28. Turner, D. F.: Selection of Protein Containing Foods to Meet Protein Requirements, J. A. M. A., to be published.

29. Williams, P. F.: Importance of Adequate Protein Nutrition in Pregnancy, J. A. M. A. **127:** 1052 (April 21) 1945. Stare, F. J., and Thorn, G. W.: Protein Nutrition in Problems of Medical Interest, ibid. **127:** 1120 (April 28) 1945. Lund, C. C., and Levenson, S. M.: Protein in Surgery, ibid. **128:** 95 (May 12) 1945.

30. Anderson, A. F., and Schloss, O. M.: Allergy to Cow's Milk in Infants with Nutritional Disorders, Am. J. Dis. Child. **26:** 451 (Nov.) 1923.

31. Hartmann, A. F.; Lawler, H. J., and Meeker, C. S.: Studies of Amino Acid Administration: II. Clinical Uses of an Enzymatic Digest of Casein, J. Pediat. **24:** 37 (April) 1944. Shohl, A. T.; May, C. D., and Shwachman, H.: Studies of Nitrogen and Fat Metabolism of Infants and Children with Pancreatic Fibrosis, ibid. **23:** 267 (Sept.) 1943. Shohl, A. T.: Nitrogen Storage Following Intravenous and Oral Administration of Casein Hydrolysate to Infants with Acute Gastrointestinal Disturbance, J. Clin. Investigation **22:** 257 (March) 1943. Cook, M. M.: Diarrheal Diseases in the Newborn Infant, J. Missouri M. A. **40:** 64 (March) 1943.

32. Weech, A. A.: Puzzles of Protein Privation: A Decade of Research into the Biologic Effects of Restricted Dietary Protein, J. Pediat. **19:** 608 (Nov.) 1941. Best, C. H., and Ridout, J. H.: The Pancreas and the Deposition of Fat in the Liver, Am. J. Physiol. **122:** 67 (April) 1938. Ravdin, I. S.: Protection of Liver from Injury, Surgery **8:** 204 (Aug.) 1940. Farr, L. E.; Emerson, K., Jr., and Fritcher, P. H.: Comparative Efficiency of Intravenous Amino Acids and Dietary Protein in Children with Nephrotic Syndrome, J. Pediat. **17:** 595 (Nov.) 1940. Also references in footnote 31.

33. Wilson, S. J., and Walzer, M.: Absorption of Undigested Protein in Human Beings: IV. Absorption of Unaltered Egg Proteins in Infants and Children, Am. J. Dis. Child. **50:** 49 (July) 1935. Ratner, B., and Gruehl, H. L.: Passage of Native Proteins Through the Normal Gastrointestinal Wall, J. Clin. Investigation **13:** 517 (July) 1934. Lippard, V. W.; Schloss, O. M., and Johnson, P. A.: Immune Reactions Induced in Infants by Intestinal Absorption of Incompletely Digested Cow's Milk Protein, Am. J. Dis. Child. **51:** 562 (March) 1936.

34. Hill, L. W.: Amino Acids as a Source of Nitrogen for Allergic Infants, J. A. M. A. **116:** 2135 (May 10) 1941.

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SATURDAY, MAY 26, 1945

## PERMISSION FOR MEETING OF HOUSE OF DELEGATES DENIED

On April 23, 1945 application for a permit to hold an annual meeting of the House of Delegates of the American Medical Association in Chicago July 23 to 25, 1945 was forwarded to the War Committee on Conventions of the Office of Defense Transportation in Washington. On May 17 the following letter was received from the secretary of that Committee:

**WAR COMMITTEE ON CONVENTIONS**
**Washington 25, D. C.**

**May 15, 1945.**

**American Medical Association**
**Dr. Olin West, Secretary**
**535 N. Dearborn Street**
**Chicago 10, Illinois**

**Dear Dr. West:**

**Your application for a permit to hold an annual meeting of House Delegates at Chicago, Illinois, July 23-25, 1945, at the Palmer House, has been reviewed by the Committee.**

**It is the consensus of the Committee that this meeting should be deferred. Therefore, permit is denied.**

**This action does not preclude your holding a meeting attended by not more than 50 persons from out of town, plus local attendance without numerical limitation.**

**Very truly yours,**
**(Signed) Frank Perrin**
**Frank Perrin, Secretary.**

Having been informed that it would not be possible to secure permission for a meeting of the House of Delegates during the month of June, it was requested in the application for a permit that a meeting might be held on July 23 to 25 with the view that those dates would antedate the movement of large numbers of troops from the European areas to the United States. It will be noted in the letter from the secretary of the War Committee on Conventions that it is the feeling of the members of that committee that the meeting of the House of Delegates should be deferred.

Application for a permit to hold a meeting at a later time will be submitted to the War Committee on Conventions.

## ARTIFICIAL KIDNEY

Abel, Rowntree and Turner[1] devised in 1912 a method by which the blood of a living animal may be submitted to dialysis outside the body and again returned to the circulation without exposure to air, infection by micro-organisms or any alteration which would be prejudicial to life. The apparatus constituted a sort of artificial kidney, and the process was called by the authors "vivi-diffusion." An extract of hirudin prepared from the heads of leeches was used to keep the blood from coagulating. Excretion of salicylic acid by the apparatus showed that 19.1 per cent of the drug injected into the femoral vein of a dog was excreted in seven hours. The principle of the method consists in connecting an artery of the animal by a cannula to an apparatus made of celloidin or other dialyzing membrane in the form of tubes immersed in a saline solution or serum, and providing for the return of the blood to the animal's body by another cannula attached to a vein. These authors were interested primarily in obtaining, by the process of dialysis of blood, a large quantity of the nonprotein amino bodies for purposes of study. They did, however, indicate therapeutic possibilities of the process.

Thalhimer[2] in 1938 reported experiments in which "exchange transfusion" was practiced. Blood from an animal rendered azotemic by a bilateral nephrectomy performed the day before the transfusion was transferred into a normal dog, and the reverse. A small amount of heparin was injected intravenously into each animal. The exchange of blood was carried out twenty to forty times. The azotemia of the nephrectomized animal was much reduced; correspondingly, azotemia was produced in the donor animal. The donor animal's condition was normal the morning after, and the blood urea had returned to a normal level. The kidneys of the donor animals, killed from one to three weeks later, were found to be normal both on gross and on microscopic examination. Thalhimer repeated the experiments of Abel and his associates, using cellophane tubes as a dialyzing membrane and heparin as the anticoagulant. In from three to five hours 200 to 700 mg. of urea nitrogen passed from the blood through the cellophane membrane into the surrounding isotonic solution of sodium chloride. Thalhimer suggested that the method could be used on human beings in certain conditions in which, as a result of accident, operation or disease, previously competent kidneys become incompetent, leading to azotemia and death.

Thalhimer, Solandt and Best[3] repeated exchange transfusion experiments on dogs, utilizing a specially designed pump which had a capacity of at least 30 liters

1. Abel, J. J.; Rowntree, L. G., and Turner, B. B.: On the Removal of Diffusible Substances from the Circulating Blood of Living Animals by Dialysis, J. Pharmacol. & Exper. Therap. **5**: 275 (Jan.) 1914.

2. Thalhimer, William: Experimental Exchange Transfusions for Reducing Azotemia: Use of Artificial Kidney for This Purpose, Proc. Soc. Exper. Biol. & Med. **37**: 641, 1938.

3. Thalhimer, William; Solandt, D. Y., and Best, C. H.: Experimental Exchange Transfusion Using Purified Heparin, Lancet **2**: 554 (Sept. 3) 1938.

an hour in each direction. Sufficient highly purified heparin was injected intravenously before and during the transfusion to prevent thrombus formation. The heparin did not appear to have any toxic action. The urea of the azotemic animal was rapidly excreted in the urine of the normal dog. The donor dog may recover completely after the termination of the experiment.

Kolff and his associates [4] working at Kampen (the Netherlands) developed a dializer consisting of a cellophane tube 25 mm. wide and 30 meters long. This tube is only partly filled with blood, giving a much larger surface area. The tube is wound spirally around the cylinder, the motion of which moves the blood from left to right. The rinsing bath contains 70 to 100 liters of tap water warmed up to 37 to 39 C. To this solution is added 0.7 per cent of sodium chloride, 1.5 per cent of glucose and 400 mg. of heparin. The patient receives a similar amount of heparin at the beginning and 100 mg. every half hour. The apparatus, according to the calculations of the authors, represents a dialyzing area of 23,000 sq. cm., the total area of the human glomeruli being 20,000 sq. cm. With this apparatus the Netherlands workers were able to reduce the blood urea and keep it at the same level for twenty-six days in a woman aged 29 who was in a state of impending uremia, with blood urea of 164 mm., blood pressure of 220/140 and uremic breath. The clinical symptoms of uremia in the course of the treatment were considerably improved after each dialysis. Unfortunately a number of intervening complications, such as pericarditis, parotitis and purulent bilateral otitis media, compromised the beneficial effect of blood washing and led to death. In their larger dialyses in this patient, 24, 40 and 35 Gm. of urea were dialyzed out respectively. The largest quantity of urea excreted by the patient in twenty-four hours in her urine amounted to 12 Gm. In addition to urea, uric acid, creatinine and residual nitrogen are being removed from the blood by dialysis. If it is desired to compensate the loss of sodium chloride or glucose from the blood, these substances can be added to the rinsing bath, since the molecules pass both in and out through the dialyzing membrane. If necessary, other substances, such as calcium, magnesium or potassium, may be added to the bath water. The authors treated 2 more patients with the artificial kidney, but both were hopeless from a clinical standpoint. However, 100 Gm. of urea was removed from 1 patient in six hours, the blood urea of the patient showing a decline from 460 to 290 mg.

From the experiences of these authors the artificial kidney of the future apparently would not find its greatest usefulness in patients with chronic nephritis and uremia; these lesions are irreversible. As originally suggested by Thalhimer, dialysis of the blood may find its application in instances in which an individual with previously competent kidneys suddenly develops loss of renal function, as after a severe burn, in a prostatic patient who develops anuria after relief of intravesicular pressure, and in anuria after operative procedures. Conceivably if the renal secretion is temporarily taken over by the artificial kidney the patient's kidneys may return to their previous competence.

4. Kolff, W. J., and Berk, H. T. J.: The Artificial Kidney: A Dialyzer with a Great Area, Acta med. Scandinav. **117**: 121 (May 27) 1944.

## NASAL STAPHYLOCOCCI AND WOUND INFECTION

Staphylococcus aureus can be isolated from the nasal cavity and skin of healthy human subjects with amazing frequency. Miles and his associates [1] have demonstrated that the nasal carrier rate for Staphylococcus aureus among people of the working class of Birmingham who come to the hospital for the first time fluctuated between 19 and 65 per cent during the period October 1942 to July 1943. The mean rate, 47.4 per cent, agrees with carrier rates that have in the past been determined mainly in hospital patients and personnel. The people studied in Birmingham consisted of three groups: (1) outpatients attending the hospital for the first time with newly inflicted wounds, (2) male inpatients in a ward with established wound sepsis and (3) the nursing staff of the same ward. The 479 outpatients had a gross nasal carrier rate of 47.4 per cent and a wrist carrier rate of 18.4 per cent. The nasal carrier rate of the 536 inpatients, calculated from their admission swabs, was 49.4 per cent. The nasal carrier rate among the nurses was significantly higher than for the newly admitted patients. The authors also demonstrated that a patient found to be a carrier on a given date had a 70 to 75 per cent probability of carrying the organism at the time of wounding, if that occurred within fourteen days of the date of swabbing. There is a similar probability that he would be capable of contaminating his wound with nasal staphylococci for at least fourteen days after that date. The carriage or noncarriage of staphylococci therefore appears to be a more or less persistent phenomenon. There appears to be a relationship between the nose and skin carriage of staphylococci; although only 24.7 per cent of nasal carriers were also skin carriers, the percentage of skin carriers among those not carrying in the nose was only 12.7. In a limited study of 16 cases the authors found by phage typing that in 15 the strains from nose and skin were identical, and in only 1 were they dissimilar. Gillespie and his associates [2] demonstrated a similar degree of association and showed that in a number of their cases the nasal and the skin strains were of the same serologic type. The greater incidence of nasal carriage and the greater profusion of staphylococci found in the nose

1. Miles, A. A.; Williams, R. E. O., and Clayton-Cooper, B.: The Carriage of Staphylococcus (Pyogenes) Aureus in Man and Its Relation to Wound Infection, J. Path. & Bact. **46**: 513 (Oct.) 1944.

2. Gillespie, E. H.; Devenish, E. A., and Cowan, S. T.: Pathogenic Staphylococci: Their Incidence in the Nose and on the Skin, Lancet **2**: 870 (Oct. 21) 1944.

of carriers as compared with that on the skin of the wrist suggests that the nose is the primary source of the cocci found on the hand.

The course of wounds on the hands of patients whose nasal and skin carrier state was determined on the day of wounding suggested to the authors a relationship between carriage on the wrist of one hand and early staphylococcus contamination of a wound on the other. This supposition finds some support in the fact that in a limited study of 18 patients similar phage types in the wound and on the skin were found in 13 patients, while in 5 they were dissimilar.

Self infection, therefore, while probably not as important or prevalent as cross infection of wounds, appears from this study to be a definite factor requiring special preventive measures in medical and surgical wards.

## MITOTIC STIMULATION OF WOUND HEALING

In 1943 Claude and Potter [1] of the Rockefeller Institute isolated chromatin threads from the resting nuclei by purely mechanical means. The frozen spleens of leukemic rats were thawed and ground gently for three minutes with an equal weight of beach sand. With the temperature below 5 C. the resulting mixture was suspended in six times its weight of isotonic solution of sodium chloride, the suspension being maintained at $p_H$ 7.4 throughout the experiment. The suspension was then centrifuged for one minute in an ordinary laboratory centrifuge (1,500 × gravity) and the resulting sediment discarded. The supernatant fluid was then submitted to ten minutes' centrifugation at the same speed. This "long run" centrifugation brought down an abundant sediment of threadlike material. The threadlike precipitate was resuspended in slightly more than an equal volume of saline solution and the "long run" centrifuging repeated two times. The entire process was completed within one hour. Rapid separation and low temperature are essential to prevent autolysis.

Microscopically the chromatin mass thus obtained was composed of filaments ranging from 0.5 to 1 micron in diameter. These were apparently identical in size and shape with the preformed chromatin strands of resting nuclei. Chemical analyses and tinctorial reactions confirmed this identity.

Aside from its general biologic interest the new chromatin preparation may have clinical value owing to its stimulating effect on the rate of mitosis when administered to experimental animals. Marshak and Walker [2] of the University of California found that, administered intravenously, Claude's chromatin extract from rat tissues hastens the rate of mitosis in the regenerating rat liver. Applied locally the chromatin preparation greatly accelerates the rate of healing of superficial skin wounds.

For a quantitative study of the rate of wound healing the California investigators [3] devised a technic for producing skin wounds of uniform depth and size. A stainless steel tube was ground at one end to make a circular cutting edge 6.6 mm. in diameter. With this trephine a depression was made in the skin on the back of the neck of an anesthetized rat. Along this line the skin was cut with a pair of iridectomy scissors through the dense connective tissue of the dermis but not through the loose connective tissue of the hypodermis. The skin thus circumscribed was lifted off without dissection. There was usually no bleeding. What little did occur was easily controlled with a small swab so that the wound did not contain blood clots. A thick solution of methacrylate polymer dissolved in toluene was then dropped on the wound, and the adjacent skin painted with the same solution to make a coat extending 3 to 5 mm. beyond the wound. On drying, contraction did not occur, as was the case with some other plastics. The plastic dressing did not adhere to the wound but did cling to the surrounding normal skin, where it acted as a splint, preventing contraction.

To study the effect of chromatin on the rate of wound healing 2 or 3 small drops of 0.12 per cent chromatin extract in saline solution was placed on the wound so as to fill the skin defect. The plastic dressing was applied over the filled wound and the adjacent normal skin. Control animals were treated in the same way except that sterile saline solution was substituted for dilute chromatin. In a typical control experiment only 3 of 15 rats showed any signs of wound healing by the fifth day. This appeared as a band of granulation tissue less than 1 mm. in width about the periphery of the wound. In contrast, 13 of the 16 chromatin treated wounds of the same series showed granulations covering from one fourth to two thirds of the entire wound area, an average of twenty-five times the average area covered in the untreated controls.

The granulation tissue in the chromatin stimulated wounds was bright red, as compared with the light pink of the untreated controls. Microscopic sections showed greater vascularization. After epithelization was complete, the elevation of the chromatin treated wound above the surrounding skin was no greater than that of the untreated controls.

Subsequently Howes [4] showed that chromatin extract administered intravenously to rabbits maximizes the rate of healing of superficial wounds of the ear. The chromatin preparation also causes greatly increased

1. Claude, Albert, and Potter, J. S.: J. Exper. Med. **77**: 345 (April) 1943.
2. Marshak, Alfred, and Walker, A. C.: Proc. Soc. Exper. Biol. & Med. **58**: 62 (Jan.) 1945.
3. Marshak, Alfred: Proc. Soc. Exper. Biol. & Med. **58**: 63 (Jan.) 1945.
4. Howes, E. L.: Personal communication.

growth rate of fibroblasts in tissue cultures. Detailed studies of its immunochemical specificity and of its stimulating effects on the rate of mitosis in regenerating internal organs are now in progress.

## Current Comment

### INDUSTRY NEEDS MEDICINE

Plant 1 of the Eastern Aircraft Division of General Motors Corporation is located at Tarrytown, N. Y. Recently the Westchester County Medical Society was invited to hold its regular monthly meeting at this plant. Two hundred and fifty members attended a most interesting session. Events included a tour of the plant, inspection of the facilities and methods employed in the medical department, and dinner in the plant cafeteria. During the formal program later a film on industrial hygiene was shown. The plant medical director described relations with the medical profession, and the chief medical consultant to the corporation described medicine's contribution to the war effort in terms of maintaining industrial manpower in good health and on the job. Here intelligent industrial management demonstrated its need for medical service. This medical requirement can and should be part of the fabric of community medical service and planning. The physicians of Westchester County realize better than before that conflict need not exist between the proper objectives of industrial medicine and the best interests of their patients. The Council on Industrial Health feels that improved standards of industrial medicine depend largely on local medical organization, education and leadership expressed through committees on industrial health in state and county medical societies. The results in Westchester County indicate that opportunity awaits mutual understanding and instruction between industry and the allied professions of medicine, dentistry, engineering and nursing.

### THE ROCKEFELLER FOUNDATION IN 1944

During 1944 the Rockefeller Foundation appropriated about $4,500,000 for public health and the medical sciences. The largest part of the budget was devoted to the International Health Division. In his presidential report, Fosdick [1] suggests that the most significant contribution of this division has been in the field of public health education. During 1944, for example, substantial sums were appropriated for fellowships and travel grants and for the support of schools of hygiene and public health nursing. A dramatic aspect of the activities of the International Health Division was the work of the typhus team under Dr. Fred L. Soper. The foundation has continued its activities also in yellow fever and in psychiatry. The accelerated program of medical education and the consequent comparative inadequacy of training of many young medical graduates has been studied by the foundation. In December 1943 the foundation made an appropriation to extend the postwar training of medical graduates returning from the armed services, and an additional sum was appropriated in 1944. The purpose of the foundation's new fellowship program is to make it possible for twenty-one leading medical schools to offer a limited number of residencies to the best of the younger medical graduates when their war work is done. The residencies thus offered are to pay stipends adequate for the individual case. One of the grants of the foundation was to the University of Michigan School of Public Health for the teaching of medical economics under Nathan Sinai, Ph.D., well known as a fluent and persistent advocate of federally controlled socialized medicine. He recently appeared in California as a guest of the governor's office, in a legislative hearing, to support compulsory sickness insurance in that state. The Rockefeller Foundation, with funds that are small compared with present day government spending, has until recently exerted a profound and on the whole beneficial influence in medical and public health fields.

1. The Rockefeller Foundation—A Review for 1944, by Raymond B. Fosdick, New York, 1945.

### WORLD AREAS OF RAPID POPULATION GROWTH

Medical practice and public health procedure will be influenced inevitably by the enormous changes in total and relative populations of various sections of the world during the next fifty years. The medical profession should have a basic conception of what present trends may mean to medical care and to the world's health. A study of areas of rapidly growing populations containing chapters on the demography of Japan, India, eastern and southern Europe, the Near East and Egypt has been published recently by the Milbank Foundation Memorial Fund.[1] India, for example, increased its population by over 50,000,000 between 1931 and 1941; the population now almost certainly exceeds 400,000,000. If this growth should continue at the rate of the relatively favorable years from 1931 to 1941, the population would double itself in fifty-seven years, i. e. reach a total of over 800,000,000. In the primarily agricultural economies both the birth and the death rates are exceedingly high in comparison with the more urbanized and economically developed countries of western Europe and the United States. Part of the dilemma facing the world is indicated by the certainty that improved sanitary, dietary and personal hygienic measures, if applied to such countries as India, would reduce the death rate with little, if any, early effect on the birth rate. The inevitable result would be an enormous increase in population which would be faced by extremely low standards of living and a greatly increased probability of starvation and epidemic disease. As pointed out by Notestein in the final chapter of this book, there is no easy solution. Certain procedures can reduce the dangers inherent in the continued rapid and enormous increase in population of some areas. The provision of medical care and public health administration to these areas of rapid growth will doubtless be a colossal problem.

1. Demographic Studies of Selected Areas of Rapid Growth, New York, Milbank Memorial Fund, 1944.

# MEDICINE AND THE WAR

## ARMY

### WOMEN DOCTORS ASSIGNED TO IMPORTANT TASKS

Eleven commissioned women doctors are serving with the U. S. Army Medical Service in the European theater of operations in capacities that range from general hospital ward surgeon to assistant medical military attaché in the American Embassy, London.

Three of these women doctors arrived in England late in 1941 at the request of the British Ministry of Health because of the critical shortage of surgeons and physicians after Dunkirk. Major Marion C. Loizeaux, Wellesley, Mass., was the first woman doctor to be commissioned in the European theater. Formerly an assistant physician at Wellesley College, she is serving on the staff of Major Gen. Paul R. Hawley, theater surgeon, as a special consultant in all matters pertaining to the medical care of the Wacs.

The two other doctors who were volunteers and are in the European theater are Capt. Eleanor Peck, Poughkeepsie, N. Y., who is assigned to the Shaef Dispensary, and Capt. Josephine Stephens of Monongahela, Pa., who is assigned to a general dispensary in Paris. A fourth, Capt. Mila Pierce, Chicago, who was a general hospital ward officer, was returned to the United States recently after she had fallen and broken her hip.

These four physicians—among twelve women doctors selected from five thousand applicants by the British Ministry of Health—were in England to greet the American Army when it arrived overseas. The four were first accepted by the U. S. Army medical service as contract surgeons and were later commissioned. Major Loizeaux was made a captain in September 1943, and the others were commissioned shortly thereafter.

Another of the twelve women doctors who served with the British as a volunteer is Major Sally Bowditch, Boston. She is assistant medical attaché to the American Embassy in London—the first woman attaché in the embassy's history. She returned to the United States at the request of Johns Hopkins University and was commissioned there in November 1943.

Included on the medical staff of a newly arrived general hospital are four women doctors: Capt. Jessie D. Read, Westfield, N. J.; Capt. Clara Raven, Youngstown, Ohio; Russian born and educated Capt. Bronislava Z. Reznick, Chicago, and 1st Lieut. Elvira C. Seno, Burlington, Wis.

Capt. Martha Howe, New York, is a recent arrival in England from the Mediterranean theater and is now a surgical ward officer in a general hospital. First Lieutenant Jean Dunham, North West Washington, D. C., anesthetist with a general hospital in England, was recently promoted to the rank of captain. Capt. Katherine E. Jackson, Fort Wayne, Ind., is an anesthetist with a general hospital. She spent five weeks doing forward area work with field and evacuation hospitals before her own unit began actual operation. A member of the twelve original women doctors who went to England as volunteers, Major Barbara Stimson, Royal Army Medical Corps, is serving with a British hospital in Italy.

There are approximately seventy-five women doctors in the U. S. Army Medical Department in all theaters.

### CHEMICAL WARFARE SERVICE DESIGNS GAS MASKS

The War Department recently announced that the Chemical Warfare Service recently designed three gas mask sizes which will fit all soldiers in the Army. Ten different head types were established, five normal and five unusual. The selection on types was made by correlating measurements representing breadth, depth and length of the face. The normal type comprises an average head and two large and two smaller sizes. The unusual types are those in which two of the principal measurements correspond with normal heads but whose third major measurement does not. It was found that 65 per cent of the soldiers measured normal medium, 19 per cent medium small and 11 per cent medium large. Four per cent of the heads were small, 3 per cent large. In the unusual size, 7 per cent had "short fat faces," the largest single category in that group. The study was carried on at Camp Sibert, Alabama, where 3,075 men representing every state in the Union, Alaska and the Philippines were tested for facial and cranium measurements. The birthplace of the soldier and the nationality of his father were taken. Facial characteristics such as fleshiness of the face, prominence of the cheek bones, pointedness of the face, prominence of the forehead, structure and shape of the nose, size of lips and whether ear lobes were attached to the face were also noted.

### HOSPITAL TRAIN UNIT RECEIVES MERITORIOUS SERVICE PLAQUE

While evacuating wounded from the Seventh Army front, members of the veteran 42d Hospital Train were notified that they were awarded the Meritorious Service Unit Plaque for "outstanding devotion to duty." The train is commanded by Major Samuel S. Gordon, Louisville, Ky., and the chief of medical service is Capt. Harold F. Goulston, New Bedford, Mass. The citation reveals that the 42d was the first hospital train to operate in southern France after the August 15 landing on the Riviera and was in continuous operation through the campaign which routed the Germans from southern and central France and on into Germany. In this period they carried 14,727 patients in forty-four round trips over a distance of 25,000 miles, as well as carrying 1,370 medical personnel and many tons of medical supplies to the Seventh Army.

Prior to the invasion of southern France the 42d operated in Italy, where it was cited by Major Gen. Arthur R. Wilson, then commanding general of the Peninsular Base Section, for evacuating wounded members of the American Fifth and British Eighth armies to rear areas. In North Africa the train took a direct part in the Sicilian campaign, receiving wounded by air evacuation at Constantine in Algeria. For services there the nurses of the unit were cited by the commanding general of the Mediterranean Base Section.

The 42d Hospital Train was activated on June 1942. Three fourths of present personnel have been with the unit since its activation at Camp Rucker, Alabama. After further training at Fort McPherson near Atlanta, Ga., the staff proceeded to North Africa, arriving there in April 1942.

### NEW ARMY GUIDE FOR INDUSTRIAL MEDICAL PROGRAM

The Preventive Medicine Service, Office of the Surgeon General, recently announced the publication of a new manual prepared by the Occupational Health Division designed to serve as a guide in standardizing the medical program of dispensaries in army industrial installations. It is listed as ASF Manual M210 and is entitled "Operating Procedures for Industrial Dispensaries."

### BEDSIDE DENTISTRY IN ARMY HOSPITALS

A portable dental unit is now being used in certain army hospitals to assure bedridden patients more complete dental care and speed convalescence. Plans are now under way to standardize this unit for all army general hospitals here. The portable dental unit carries equipment for a wide variety of dental operations from simple dental prophylaxis to treating fractured jaws and making complete new dentures.

## ARMY AWARDS AND COMMENDATIONS

### Lieutenant Colonel Elmer M. Smith

Lieut. Col. Elmer M. Smith, formerly of State Center, Iowa, was recently awarded the Legion of Merit for "exceptionally meritorious conduct in the performance of outstanding services in Italy from April 1 to Sept. 15, 1944. Confronted with the responsibility of malaria control for the headquarters and seven groups of the 306th Fighter Wing, Lieutenant Colonel Smith, as wing surgeon, accomplished outstanding work in combating malaria. The area occupied by the flying fields of the wing were considered among the worst malaria districts in Europe, where 99 per cent of the local Italian population had had malaria at one time or another. Lieutenant Colonel Smith immediately organized a survey of the district and visited the swamps to investigate the possibility of draining them. By his hard and thorough work, tools, screening, extra repellent and freon bombs were immediately secured at a time when they were vitally needed. In order to oil and clean the scores of swamps and streams in the area before the summer months he adopted the use of airplanes and chemical warfare equipment for spraying large areas and the use of special plows for the digging of swamp drainage ditches. His capable organizing ability in making malaria surveys, in gathering tools and labor to drain the marshes and in instituting and advertising malaria discipline among troops assured the malaria control projects of success, thereby reflecting great credit on himself and on the Medical Corps of the Army of the United States." Dr. Smith graduated from the State University of Iowa College of Medicine, Iowa City, in 1935 and entered the service Oct. 1, 1940.

### Captain Lal. D. Threlkeld

The Bronze Star was recently awarded to Capt. Lal. D. Threlkeld, formerly of Syracuse, N. Y., "for meritorious service in connection with military operations against an enemy of the United States in France, Belgium, Holland and Germany from Aug. 1, 1944 to Jan. 30, 1945. When his squadron spearheaded a drive into Brittany, France, Captain Threlkeld displayed great ingenuity and remarkable stamina in treating many cases while on the move and in caring for all the wounded until evacuation was practicable, so that fatalities were kept to a minimum. His thorough professional knowledge and personal interest in the welfare of every member of his unit have greatly contributed to the efficiency and morale of the squadron and reflect credit on Captain Threlkeld's character as an officer of the Medical Corps of the Army." Dr. Threlkeld graduated from the University of Oklahoma School of Medicine, Oklahoma City, in 1940 and entered the service in June 1942.

### Lieutenant Colonel H. D. Chalke

The United States of America Typhus Commission Medal was recently awarded to Lieut. Col. H. D. Chalke, assistant director of hygiene, Royal Army Medical Corps (British). The citation read "In connection with the work of the United States of America Typhus Commission during the epidemic of typhus fever in Naples and southern Italy in the winter of 1943-1944, Colonel Chalke had heavy responsibilities for the extension and application of typhus control measures pertaining to British troops and involving civilians in areas under British control. A particularly important part of these activities, carried out by him with notable success under the most difficult conditions, was the disinfection of refugees entering Italy from across the Adriatic. The services rendered by Colonel Chalke were an essential element in preventing spread of typhus in southern Italy."

### Major Ira Teicher

Major Ira Teicher, formerly of Brooklyn, was recently awarded the Bronze Star. The citation accompanying the award read "for meritorious service in action during the period Jan. 25, 1945 to Feb. 6, 1945. Commanding the —— Portable Surgical Hospital, Captain Teicher performed 211 operations, 145 of which were in a three day period of continuous work. The combination of surgical skill and administrative ability exhibited by Captain Teicher under extreme conditions reflects great credit on himself and the armed forces of the United States." Dr. Teicher graduated from Cornell University Medical College, New York, in 1936 and entered the service in June 1942.

### Captain Roy S. Averill

The Silver Star and an Oak Leaf Cluster were recently awarded to Capt. Roy S. Averill, formerly of Canonsburg, Pa., for gallantry. First cited for his heroism at Maknassey in March 1943, when his battalion was attacking a strongly fortified point, for which he was presented the Silver Star, Captain Averill in January 1944 near Cassino performed the action winning him the Oak Leaf Cluster in lieu of a second Silver Star. He carried three units of blood plasma through two unmarked mine fields under artillery fire and direct observation and administered treatment under fire, after which he helped the wounded men to the battalion aid station. Dr. Averill graduated from Western Reserve University School of Medicine, Cleveland, in 1940 and entered the service in July 1941.

### Captain Edward O. Groeber

Capt. Edward O. Groeber, formerly of Brooklyn, was recently awarded the Bronze Star for meritorious service in combat from May 21 to 25, 1944, in Italy. The citation reads "With great efficiency Captain Groeber supervised the establishment and maintenance of lines of evacuation, over trackless stretches of mountains, using with great ingenuity mules and untrained Italian soldiers, as well as regularly assigned litter bearers. At the same time he rendered personally the highest degree of professional medical and surgical care." Dr. Groeber graduated from Long Island University College of Medicine, Brooklyn, in 1931 and entered the service June 19, 1942.

### Captain James Gordon

Special commendation was recently extended to Capt. James Gordon, formerly of New York and now with the 155th Station Hospital "somewhere in the South Pacific," for splendid assistance rendered by his generous, willing and professionally excellent contribution to the dermatologic section of his unit. "By his professional ability and his eagerness to cooperate, this officer has set a high standard and has reflected credit on himself, his profession and his organization," the commendation read. Dr. Gordon graduated from New York University College of Medicine, New York, in 1929 and entered the service Aug. 18, 1942.

### Captain Benjamin L. Falcone

A Certificate of Merit was recently awarded to Capt. Benjamin L. Falcone, formerly of Bridgeport, Pa. The citation read "From May 25, 1944 to June 29, 1944, as a medical officer with the First Army Medical Detachment, Captain Falcone landed on the continent on D day plus two and rendered valuable service in the treatment of large numbers of Allied and enemy casualties under difficult and trying circumstances." Dr. Falcone graduated from Hahnemann Medical College and Hospital of Philadelphia in 1936 and entered the service Sept. 3, 1942.

### Captain William S. M. Ling

The Bronze Star was recently awarded to Capt. William S. M. Ling, formerly of New York, for his heroism on the Anzio beachhead in Italy. Dr. Ling, a physician of Chinese extraction, interned at Misericordia Hospital, Manhattan, and served in North Africa, Tunisia, Salerno and northern Burma as well as in Italy. He graduated from the University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, in 1940 and entered the service Sept. 1, 1941.

### Captain Donald W. Cheff

Capt. Donald W. Cheff, formerly of Wilmington, Del., was recently awarded the Bronze Star for heroic achievement in action during the Leyte campaign. He is company commander of the medical battery of the famed 77th Infantry Division, which also participated in the invasion of Guam. Dr. Cheff graduated from the University of Nebraska College of Medicine, Omaha, in 1937 and entered the service June 20, 1942.

### MEDICAL ADMINISTRATIVE CORPS OFFICERS

Typical illustrations of the heroic part being played by Medical Administrative Corps officers in this war is found in the recent citations which name Lieut. Paul F. Kerkhoff and Lieut. Allen E. Meeks for their gallant actions under fire.

Lieutenant Kerkhoff, Cincinnati, was awarded the Silver Star for his heroism with the 45th Armored Medical Battalion of the 3d Armored Division during the Ardennes breakthrough in December. One ambulance was knocked out and the medical supply trucks were isolated. Lieutenant Kerkhoff organized a group that went through heavy fire to rescue the trucks, which contained valuable life-saving cargo.

Lieutenant Meeks, San Bernardino, Calif., was awarded the Bronze Star for his service as assistant battalion surgeon. "In many instances," the citation reads, "this diligent officer risked his life in evacuating the wounded while exposed to heavy, small arms, mortar and artillery fire. His aggressive, energetic actions and untiring devotion to duty saved the lives of many men."

The work of the Medical Administrative Corps officers is not restricted to the combat zones. They handle administrative work in almost every phase of the Medical Department's activities, thereby permitting doctors to confine most of their activities to professional duties. The growth in the past three years of the Medical Administrative Corps from a strength of 75 to 17,000 is an indication of the extent of their help to the Medical Corps.

### RATE OF RECOVERY FROM CHEST WOUNDS

In a recent release from the War Department, Major Gen. Norman T. Kirk, Surgeon General of the Army, reported that the rate of recovery from chest wounds is triple that of the first world war. The death rate of wounded men who lived long enough to reach surgery in the first world war was 24 per cent. Now it is 8, and this low rate has been achieved in spite of the fact that chest wounds are more serious in this war because of the increase in bomb fragments. The teams of young surgeons on the battle lines believe that if the wounded man can be got alive to an evacuation hospital, the surgical station closest to the front lines, the chances are that he will live.

### ARMY DOCTORS TO CONSERVE X-RAY FILM

According to the Office of the Surgeon General, Army Medical Officers have been ordered to conserve x-ray films and photographic paper because of serious civilian and military shortages of these materials. Medical case histories will continue to be prepared on all troops being redeployed, but routine chest x-rays will not be made. This step will not be necessary, the Office of the Surgeon General explained, because chest x-rays were made of these men when they went overseas and the Army has kept a critical eye on them ever since. However, if the redeployment examination indicates tuberculosis or any other chest disease, an x-ray will be made promptly.

### ARMY HAS NEW HEALTH EDUCATION UNIT

A new health education unit was recently set up as part of the Preventive Medicine Service, Office of the Surgeon General, U. S. Army, to develop educational material for the various divisions of the Preventive Medicine Service. Capt. Granville W. Larimore is chief of the new unit.

### MERITORIOUS SERVICE PLAQUE AWARDED

The 1777th Service Command Unit, Schick General Hospital, Clinton, Iowa, was recently awarded the Meritorious Service Unit Plaque for "superior performance and devotion to the hospital duties performed during the last sixteen months."

## NAVY

### NAMED HEAD OF MUSEUM COMMITTEE

Rear Admiral Harold W. Smith, chief of the research division of the Bureau of Medicine and Surgery, was recently designated chairman of a Medical Museum Committee and curator for the medical department in conformity with the projected plan for establishment of a naval museum in Washington. The appointment was made by Vice Admiral Ross T. McIntire, Surgeon General of the Navy. The Medical Museum Committee is responsible for the selection, collection, preparation and preservation of trophies, relics, pictures, models, dioramas and other materials of historical interest for exhibit in the contemplated naval museum in Washington.

### NAVAL HOSPITAL HEADS MAY AWARD PURPLE HEART

The Secretary of the Navy recently authorized the presentation of the Purple Heart award by medical officers in command of all hospitals within the continental limits in order to eliminate delay between time of wound and award presentation. In addition, fleet commanders are authorized to delegate authority to award the Purple Heart "to commanding officers of such hospital ships, advance base or other hospitals within their commands as they may deem necessary for this purpose."

### HISTORY OF PSYCHIATRY

Capt. Forrest M. Harrison, chief of the neuropsychiatric division of the National Naval Medical Center, Bethesda, Md., was recently ordered to the Bureau of Medicine and Surgery on a special assignment to write the history of psychiatry in the Navy in World War II.

### NAVY AWARDS AND COMMENDATIONS

#### Captain Rolland R. Gasser

Capt. Rolland R. Gasser, formerly of Brooklyn, was recently awarded the Bronze Star "for meritorious service to the government of the United States as medical officer in command of a fleet hospital in the South Pacific area from March 31, 1944 to April 7, 1945. During this period Captain Gasser displayed exceptional ability in handling the many detailed medical problems which arose and worked tirelessly to establish and maintain excellent operating conditions throughout his command. By his initiative and thorough knowledge of medical administration he effected an efficient hospital service for the sick and wounded in the South Pacific and evacuees from adjacent areas. His leadership and professional skill were in keeping with the highest traditions of the United States Naval Service." Dr. Gasser graduated from Jefferson Medical College of Philadelphia in 1914 and has been in the service since June 11, 1917.

#### Lieutenant Commander Gerald O. Poole

Lieut. Comdr. Gerald O. Poole, formerly of Lindamere, Del., was recently cited by Admiral Harold R. Stark. The citation accompanying the award read "Your performance of duty prior to and during the invasion of France on June 6, 1944 has been brought to my attention. As senior medical officer at a U. S. naval advanced amphibious base your professional skill was responsible for averting a serious delay in training programs and preparations for the invasion. When, shortly before D day, food poisoning broke out involving in varying degrees some 500 officers and men of both base and small boat personnel,

your untiring devotion in caring for these men and your thorough analysis of the cause of the outbreak enabled all personnel to resume their duties quickly. For your professional skill and your devotion to duty you are hereby commended. This commendation carries with it the privilege of wearing the commendation ribbon." Dr. Poole graduated from Hahnemann Medical College and Hospital of Philadelphia in 1931 and entered the service Oct. 19, 1942.

### Lieutenant Commander Clinton P. O'Connell

The Navy and Marine Corps Medal was recently presented to Lieut. Comdr. Clinton P. O'Connell, formerly of Paterson, N. J., for "heroism displayed in attending the wounded and evacuating casualties while under enemy fire during amphibious operations in the Southwest Pacific Area from April 1944 to July 1944. A member of the surgical unit of the Seventh Amphibious Force accompanying assault waves, Lieutenant Commander O'Connell, by his courage and skill in providing medical care, helped save many lives and aided in making possible the transportation of casualties over greater distances than ever attempted previously." Dr. O'Connell graduated from Columbia University College of Physicians and Surgeons, New York, in 1932 and entered the service July 28, 1941.

### Lieutenant James C. Owens

The Bronze Star was recently awarded to Lieut. James C. Owens, formerly of Beloit, Wis., who was cited for his heroism and his outstanding professional ability during an amphibious assault operation against Saipan and Marianas islands. Through his efforts and under adverse conditions when other medical units were disorganized, lives of many casualties were saved. Dr. Owens graduated from Marquette University School of Medicine, Milwaukee, in 1942 and entered the service March 8, 1943.

### Commander John F. Woodward Jr.

The Navy Commendation Ribbon for outstanding performance of duty as senior medical officer at the U. S. Naval Dispensaries at Oran and Naples was recently awarded to Comdr. John F. Woodward Jr., formerly of New York. The citation accompanying the award read, in part, "Your thorough and untiring efforts contributed materially to the maintenance of a high standard of health and well being among the personnel of the fleet and supporting shore establishments and to the prompt and efficient handling of battle casualties during the amphibious invasions of Italy and southern France." Dr. Woodward graduated from the University of Virginia Department of Medicine, Charlottesville, in 1928 and entered the service in May 1942.

### Lieutenant Commander Victor S. Falk

The Silver Star was recently awarded to Lieut. Comdr. Victor S. Falk, formerly of Wauwatosa, Wis., for treating wounded Marines under fire on Guadalcanal. The citation read, in part, "for conspicuous gallantry and intrepidity while serving with the First Marine Aircraft Wing during action against enemy Japanese forces on Guadalcanal, Solomon Islands, on the night of Oct. 13-14, 1942." Dr. Falk graduated from the University of Wisconsin Medical School, Madison, in 1939 and entered the service Nov. 28, 1941.

### Lieutenant Robert M. Collins

The Navy and Marine Medal was recently awarded to Lieut. Robert M. Collins, formerly of Council Bluffs, Iowa, for "distinguishing himself by meritorious achievement and service in connection with operations in the Southwest Pacific as a member of the surgical unit of the 7th Amphibious Force during the period of April 1944 to July 1944." Dr. Collins graduated from the University of Nebraska College of Medicine, Omaha, in 1931 and entered the service Sept. 7, 1942.

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## MISCELLANEOUS

### HOSPITALS NEEDING INTERNS AND RESIDENTS

The following hospitals have indicated to the Council on Medical Education and Hospitals that they have not completed their house staff quota allotted by the Procurement and Assignment Service:

(Continuation of list in THE JOURNAL, May 12, page 137)

ILLINOIS

Columbus Hospital, Chicago. Capacity, 180; admissions, 3,501. Reverend Mother M. Grace, R.N., Superintendent (2 interns).

Mother Cabrini Memorial Hospital, Chicago. Capacity, 144; admissions, 3,931. Mother Agnes, R.N., Superintendent (2 interns).

Oak Park Hospital, Oak Park. Capacity, 182; admissions, 5,479. Sister St. Colette, Superintendent (intern, July 1).

KANSAS

University of Kansas Hospitals, Kansas City. Capacity, 400; admissions, 7,606. Dr. J. Harvey Jennett, Medical Director (resident—anesthesia; assistant resident—surgery, July 1, disqualified for military service).

KENTUCKY

Louisville General Hospital, Louisville. Capacity, 587; admissions, 9,971. Dr. John Walker Moore, Medical Director (resident—medicine; 2 assistant residents—surgery).

MASSACHUSETTS

Boston City Hospital, Boston. Capacity, 2,537; admissions, 35,559. Dr. James W. Manary, Medical Director (resident—dermatology, July 1, disqualified for military service).

MISSOURI

St. Louis City Hospital, St. Louis. Capacity, 1,104; admissions, 14,098. Dr. Leo J. Wade, Medical Director (resident—pathology, July 1, disqualified for military service).

NEW YORK

Herman M. Biggs Memorial Hospital, Ithaca. Capacity, 250; admissions, 204. Dr. N. Stanley Lincoln, Superintendent (residents—tuberculosis and thoracic surgery).

St. John's Riverside Hospital, Yonkers. Capacity, 220; admissions, 4,429. Mr. S. Chester Fazio, Superintendent (4 interns, February 1, 1946).

OHIO

Glenside Hospital, Cleveland. Capacity, 135; admissions, 3,411. Mr. A. B. Harris, Superintendent (resident—mixed, disqualified for military service).

TENNESSEE

Nashville General Hospital, Nashville. Capacity, 337; admissions, 6,586. Mr. T. F. Connally, Administrator (intern, July 1).

UTAH

St. Mark's Hospital, Salt Lake City. Capacity, 238; admissions, 4,838. Mrs. Olive V. Wardrop, Superintendent (intern).

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### WARTIME GRADUATE MEDICAL MEETINGS

The following subjects and speakers for Wartime Graduate Medical Meetings have just been announced:

#### California

U. S. Naval Air Training Station, San Diego: Rh Factor, Capt. George Macer, June 1.

Camp Haan, ASF Regional Hospital, Riverside: Thoracic Surgery, Dr. John Jones and Lieut. Comdr. J. E. Dailey, June 5.

Torney General Hospital, Palm Springs: Management of Simple Skin Diseases, Lieut. Col. Everett R. Seale, June 5.

AAF Regional Hospital, Santa Ana Army Air Base: Blood and Blood Substitutes, Lieut. Comdr. W. M. Cashman, June 5.

Station Hospital, Camp Cooke, Lompoc: Internal Derangements of the Knee, Dr. John C. Wilson, June 6.

Hoff General Hospital, Santa Barbara: Internal Derangement of the Knee, Dr. John C. Wilson, June 6.

U. S. Naval Hospital, San Diego: Diabetes, Drs. H. F. West and J. W. Sherrill, June 7.

Birmingham General Hospital, Van Nuys: Spondylitis, Major A. J. Present, June 13.

U. S. Naval Hospital, Santa Margarita Ranch: Surgery of Traumatic Urinary Tract, Lieut. Comdr. John B. Wear, June 14.

U. S. Naval Hospital, Corona: Diabetes, Drs. H. F. West and J. R. Sherrill, June 14.

U. S. Naval Air Training Station, San Diego: Dentistry, Comdr. E. P. Garvey (DC).

# ORGANIZATION SECTION

## Washington Letter

*(From a Special Correspondent)*

May 21, 1945.

### Drug Cartels and the National Health

Following a warning by Wendel Berge, assistant U. S. attorney general, that drug cartels and monopolies have seriously retarded national health, a House subcommittee investigating aid to the physically handicapped has proposed war on monopolies and cartels in industries relating to health. Elimination of such monopolies, said Mr. Berge, would be "one of the most constructive tasks of our generation." He said that the "time had come for Congress to consider the cartel problem in all its aspects." He asserted that monopoly practices in the medicinal and pharmaceutical field led to suppression of research data, prevented introduction of improved processes and products and kept outsiders from engaging in research. He declared that "because of artificial and exorbitant price structures the low income groups in particular have been unable to obtain the benefits of advances in science or better physical aids." He stated, among his charges, that: 1. Thirty-four thousand Americans need spectacles and cannot buy them because of controlled prices. 2. Despite an annual world death of more than 3 million people, 500 million sufferers from malaria were dependent in prewar days on quinine obtained from a few thousand acres of cinchona trees in Java. 3. Production and distribution of all types of surgical supplies is controlled by a monopoly group. 4. The public has been forced to pay "excessive and arbitrary prices by a monopoly controlling the vitamin D industry." 5. A "small ring of producers" of insulin "exploited" 2 million sufferers of diabetes in this country by "imposing arbitrary prices and unreasonable conditions of distribution." 6. A plastic, methyl methacrylate, was sold to industrial concerns for 85 cents a pound and to dental users for $45 a pound, although "the dental profession soon learned that there was no difference in the material." 7. German I. G. Farben-Industrie once attempted to sell the secret of Bayer 205, a cure for sleeping sickness, for restoration of Germany's lost African colonies.

The subcommittee also heard Henry Miller, director of the Trade Practices Conference of the Federal Trade Commission, and R. P. Whiteley of the FTC legal staff, on advertising of drugs, eye glasses and hearing aids.

### Lay Control of Veterans Administration Hospitals

Representative Walter Judd of Minnesota, a physician, has charged that Veterans Administration hospitals are too much controlled by laymen, which he says will "inevitably develop whenever and wherever government bureaus under nonmedical men tell doctors how to practice." It has been pointed out that the House Veterans Committee under Chairman John Rankin of Mississippi, now investigating the Veterans Administration, does not include any physicians, fifteen of the twenty-one members being lawyers. This fact has been criticized editorially, one paper stating that none of the members have any obvious qualifications "to pass judgment on highly technical questions of medical expertness or hospital management. Picture the indignation among Congressmen if a committee of doctors should undertake to dissect their performance as legislators." Also criticized were the Rankin sponsored visits to veterans' hospitals, which were described as "Cook's tours." It has also been pointed out that Representative Rankin is the strongest Congressional defender of Veterans Administrator Brigadier General Hines. The latest development in the hearing is a contempt citation by the committee against a New York reporter for refusal to tell the names of Veterans Administration officials who supplied information used in his articles criticizing veterans' hospital care. President Truman has denied that there will be a shake-up in the agency or that he will replace General Hines by former Senator Bennett Champ Clark of Missouri.

### Institute at Ann Arbor for Placement of Handicapped

Medical, industrial, social welfare and labor groups will be represented at the five day institute for discussion of the War Manpower Commission's selective placement program for the handicapped at the University of Michigan, Ann Arbor, May 28 through June 1. An important phase will be panel discussions on placement of returning veterans who have suffered severe service connected disabilities. The conference will lay the groundwork for an expanded program to disabled through local USES offices. Among the speakers will be Holland Hudson, director of rehabilitation for the National Tuberculosis Association; Dr. W. C. Strang of the Civil Service Commission; Dr. F. J. Brady of the U. S. Public Health Service; Dr. Raymond Hussey, dean of the School of Occupational Health, Wayne University; Dr. Carl Peterson, Secretary, Council on Industrial Health, American Medical Association; Dr. Clarence Selby, medical director of General Motors; Dr. H. L. Krieger, medical director of the Ford Motor Company; Capt. H. H. Montgomery of the Bureau of Medicine and Surgery, U. S. Navy, and Col. E. G. Solomon of Selective Service.

### Amputation Cases in Army Hospitals

Surg. Gen. Norman T. Kirk announces that on May 1 there were approximately 11,000 amputation cases in army hospitals in this country, including cases already discharged. He said there are still no "basket cases," a term used to describe a person who has lost both arms and both legs. There are 6 amputees who have lost three extremities and 1 case of a nonbattle casualty who lost part of four limbs through freezing after an airplane crash. About 5 per cent of the patients have lost more than one limb, General Kirk said. Of these, 77 per cent are leg amputations, of which 49 per cent are below the knee and about 28 per cent above the knee. Half of the arm cases are below the elbow. Almost 4,000 of the amputees have been discharged to civilian life. Some soldiers are remaining in the service and have been assigned to assist in training other amputees.

### Red Cross to Increase Personnel in the Pacific

In a statement issued at Pearl Harbor and received here, Basil O'Connor, national chairman of the Red Cross, said that the organization will double its facilities in the Pacific and increase to 60,000 nurses and 32,000 other workers within a year. O'Connor is en route to the Philippines for discussions with Gen. Douglas MacArthur and later with Fleet Admiral Chester W. Nimitz. "The Red Cross is now working on terra firma in Europe, but here we must leap forward from island to island," he said.

### Capital Notes

Reports indicate that returns in the national cancer campaign to raise $5,000,000 are exceeding expectation but that continued support is required.

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Despite reports of an anticipated increase in malaria through return of men from disease infected war areas, the Maryland Bureau of Communicable Diseases reports that it has experienced no such increase.

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Chairman Bilbo of the Senate District Committee has introduced in the Senate a bill to strengthen District of Columbia contagious disease control. A companion measure was placed before the House earlier by Representative McMillan, Democrat of South Carolina.

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Although nineteen blood donor centers in the country were to close May 19, the District of Columbia center will continue with renewed effort, reports Red Cross National Chairman O'Connor.

# Bureau of Information

## COUNTY SUMMARY SHEETS FROM KENTUCKY, MISSOURI AND NEW MEXICO

Kentucky, through Dr. P. E. Blackerby, secretary of the Kentucky State Medical Association, Missouri, through Mr. T. R. O'Brien, executive secretary of the Missouri State Medical Association, and New Mexico, through Dr. L. B. Cohenour, secretary of the New Mexico Medical Society, have returned completed county summary sheets.

### Kentucky

| County [1] | Principal Cities [2] | Population | Physicians Under 65 | Persons per Physician | Persons per Telephone [3] |
|---|---|---|---|---|---|
| Adair | | 15,502 | 4 | 3,875 | 50 |
| Barren | | 24,545 | 7 | 3,506 | 17 |
| | Glasgow | 5,815 | | | |
| Bell | | 39,762 | 16 | 2,485 | 38 |
| | Middlesborough | 11,777 | | | |
| | Pineville | 3,882 | | | |
| Boyd | | 42,800 | 18 | 2,378 | 10 |
| | Ashland | 29,537 | | | |
| Christian | | 35,813 | 16 | 2,238 | 19 |
| | Hopkinsville | 11,724 | | | |
| Fayette | | 77,085 | 67 | 1,151 | 9 |
| | Lexington | 49,304 | | | |
| Pulaski | | 31,294 | 12 | 2,608 | 30 |
| | Somerset | 6,154 | | | |
| Scott | | 12,773 | 4 | 3,193 | 14 |
| | Georgetown | 4,420 | | | |
| Union | | 17,083 | 4 | 4,271 | 19 |
| | Morganfield | 3,079 | | | |
| Webster | | 16,149 | 7 | 2,307 | 27 |
| | Providence | 4,397 | | | |

### Missouri

| County [1] | Principal Cities [2] | Population | Physicians Under 65 | Persons per Physician | Persons per Telephone [3] |
|---|---|---|---|---|---|
| Atchison | | 10,410 | 3 | 3,470 | 5 |
| Barry | | 19,435 | 5 | 3,887 | 13 |
| | Monett | 4,395 | | | |
| Bollinger | | 9,643 | 3 | 3,214 | 27 |
| Boone | | 33,128 | 25 | 1,325 | 6 |
| | Columbia | 18,390 | | | |
| Butler | | 29,526 | 8 | 3,691 | 21 |
| | Poplar Bluff | 11,163 | | | |
| Clark | | 8,770 | 1 | 8,770 | 6 |
| Dallas | | 9,429 | 2 | 4,715 | 21 |
| Howard | | 10,423 | 5 | 2,085 | 7 |
| | Fayette | 2,608 | | | |
| Jackson | | 485,893 | 302 | 1,609 | 6 |
| | Kansas City | 399,178 | | | |
| | Independence | 16,066 | | | |
| Miller | | 12,354 | 1 | 12,354 | 11 |
| | Eldon | 2,590 | | | |

### New Mexico

| County [1] | Principal Cities [2] | Population | Physicians Under 65 | Persons per Physician | Persons per Telephone [3] |
|---|---|---|---|---|---|
| Bernalillo | | 69,794 | 52 | 1,342 | 11 |
| | Albuquerque | 35,449 | | | |
| Colfax | | 15,194 | 5 | 3,039 | 16 |
| | Raton | 7,607 | | | |
| Curry | | 20,452 | 11 | 1,859 | 19 |
| | Clovis | 10,065 | | | |
| De Baca | | 4,825 | 2 | 2,413 | 56 |
| Dona Ana | | 27,128 | 5 | 5,426 | 27 |
| | Las Cruces | 8,385 | | | |
| Lea | | 16,311 | 4 | 4,078 | 24 |
| | Hobbs | 10,619 | | | |
| Rio Arriba | | 20,604 | 5 | 4,121 | 261 |
| San Juan | | 10,308 | 1 | 10,308 | 33 |
| San Miguel | | 23,099 | 4 | 5,775 | 34 |
| | Las Vegas | 6,421 | | | |
| Socorro | | 8,658 | 3 | 2,886 | 69 |
| | Socorro | 3,712 | | | |

1. Bureau of Census, estimated population 1943.
2. Bureau of Census, population 1940.
3. Based on 1940 figures, American Telephone and Telegraph Company.

Data from five representative counties of each state are presented in the accompanying table. The column giving the number of persons per telephone is used as one index of the economic status of the area. Many physicians over 65 years of age are carrying on large practices and are doing much to maintain the health of communities. They are not included in computing physician population ratio, however, as the future needs of the communities will be largely dependent on younger physicians.

A current knowledge of needs of communities for doctors is essential if adequate help is to be given veteran medical officers in their problems of medical practice. These needs can be indicated on the summary sheets under "Remarks" by the state and county secretaries and are then available to inquiring medical officers. Frequent reports from state and county medical societies about needs of communities for doctors will help maintain current files and will increase the service of the Bureau.

With the information available on a completely filled out summary sheet, it is readily possible for an interested medical officer to make an initial selection of areas in which he might like to practice. Since vacancies are held open in many communities for doctors now in military service, further investigation by direct correspondence with state and county medical societies will always be necessary to insure an accurate report of the needs of individual communities.

# Medical Legislation

## MEDICAL BILLS IN CONGRESS

### EMIC Program

An additional appropriation of $44,189,500 will be made available for the EMIC program by H. R. 3199, a bill making appropriations for the Department of Labor, the Federal Security Agency and related independent agencies for the fiscal year ending June 30, 1946. In its report on the bill, which has now passed the House, the Committee on Appropriations referred to prior efforts to prevent what it described as "discrimination between persons licensed under state law to practice obstetrics." The committee thought that some progress had been made in "eliminating the discrimination" but suggested an additional proviso to the language inserted by the committee last year, as follows: "Provided further, That a state plan shall include standards for professional services prescribed by the state health agency within the limitations contained in this title and such standards so prescribed shall be approved by the chief of the Children's Bureau." On motion of Representative Judd, Minnesota, this proviso was amended to read "Provided further, That any state plan which provides standards for professional obstetric services in accordance with the laws of the state shall be approved by the chief of the Children's Bureau."

### Veterans Administration

Representative Miller, Nebraska, has introduced H. R. 3254 to authorize the furnishing in private facilities of medical and hospital treatment to certain veterans. This will be accomplished by defining the term "Veterans Administration facility" as used in the existing law to include any private facility for which the Administrator of Veterans' Affairs may deem it necessary to contract in order to provide medical and hospital treatment (1) in emergency cases; (2) for veterans of any war, in any case where neither a facility under the exclusive jurisdiction of the Veterans Administration nor a government facility utilized by the Veterans Administration is within a reasonable distance of the place of residence of the veteran; (3) for women veterans of any war, and (4) for veterans of any war in the territories and possessions.

### Food and Drugs

A bill introduced by Representative Lea, California, H. R. 3266, proposes to amend the Federal Food, Drug and Cosmetic Act by providing for the certification of batches of drugs composed wholly or partly of any kind of penicillin or any of its derivatives. The language of the bill is similar to that of the existing law safeguarding the purity of insulin.

### U. S. Employees' Compensation Act

A subcommittee of the Senate Committee on Education and Labor held a hearing, May 16, on S. 178, a bill to permit chiropractors to treat the beneficiaries of the U. S. Employees' Compensation Act. Only witnesses who supported the bill testified, including the sponsor of the bill, Senator Murdock, Utah, Representative Tolan, California, who has introduced a companion bill in the House, representatives of the National Association of Letter Carriers, of the National Federation of Post Office Clerks, of the Rural Mail Carriers' Association, and the Director of Education, National Chiropractic Association, John J. Nugent, D.C. Witnesses in opposition to the bill will be heard on a later date. The following members of the Senate Committee on Education and Labor comprise the subcommittee: Senators Fulbright, Arkansas, chairman; Walsh, Massachusetts; Chavez, New Mexico; Smith, New Jersey, and Morse, Oregon.

## STATE LEGISLATION

### Alabama

*Bill Introduced.*—H. 148 proposes to appropriate $150,000 annually for the next biennium to the state board of health for acquiring and distributing whole blood and blood plasma to persons in need thereof.

### Florida

*Bills Introduced.*—S. 435, to amend the medical practice act, proposes, among other things, to make it unlawful (1) for any physician to fail or neglect to register by January 1 annually and to provide a penalty of $50 for such an offense; or (2) for any person to sell or fraudulently obtain or furnish any medical diploma, license, record or registrations or to practice medicine under such fraudulent credentials, or advertise to practice medicine under a name other than his own. S. 436, to amend the medical practice act, proposes (1) to make it the specified duty of the state board of health, of all peace officers and of all prosecuting attorneys to enforce the provisions of the act and (2) to authorize the state board of medical examiners to proceed by injunction to restrain any continued violation of the act. H. 664 proposes to prohibit the operation of a private nursing home in counties having a population of from 65,000 to 74,000 unless licensed to do so by the state board of health.

### Illinois

*Bills Introduced.*—S. 466 and H. 649, to amend the medical practice act, propose that students matriculating or entering on a course of study of any system or method of treating human ailments without the use of drugs or medicines and without operative surgery during the years 1940 to 1947, inclusive, shall be entitled to examination for licensure if they have graduated from a healing art school and if the course of instruction pursued therein has not been less than thirty-two months. Under the present law the course of instruction must not be less than thirty-six months.

### Massachusetts

*Bills Introduced.*—S. 551 proposes to create a special commission to study the advisability of establishing a state university, including a medical and dental school. S. 554, to amend the medical practice act, proposes that the authority approving medical schools shall consist, in addition to its present members, of an osteopathic member of the board of registration in medicine and a layman. H. 1905 proposes to create a special commission of two senators, four representatives and three persons appointed by the governor to investigate all institutions, other than educational, maintained by the commonwealth with respect to the conduct of such institutions, the adequacy of their facilities and such other matters as the commission may deem advisable. H. 1923 proposes to provide what is designated as a voluntary system for the payment of hospital, surgical operation, sickness and bodily injury and maternity benefits to employees.

### Texas

*Bills Introduced.*—H. Con. Res. 34 proposes to create a state commission to make a comprehensive survey of existing hospital facilities and the need, if any, for additional hospitals, clinics and health services and to serve as the state agency for executing the hospital program that may be enacted by the federal Congress. S. 216 proposes to require the state department of health to survey hospital facilities, health centers, clinics and related public health needs as provided for in S. 191 now pending before the federal Congress. The bill proposes to authorize the board of health to make and/or approve applications for funds as may be provided in any future federal law.

# Official Notes

## DOCTORS LOOK AHEAD

Radio broadcasts by the American Medical Association under the title Doctors Look Ahead and other titles have emphasized medical progress. There remains however the unfinished business which confronts the medical profession about which little is said. Doctors Look Ahead therefore will broadcast a program devoted exclusively to looking ahead at the challenge of tomorrow, at the unfinished business, at the progress that has not been made. This program will be broadcast May 26 and the guest speaker will be Dr. Morris Fishbein, Editor of THE JOURNAL.

Other programs in the Doctors Look Ahead series scheduled in the next four weeks are as follows:

June 2. Fit to Live: A program devoted to the topic of fitness as distinguished from health and illustrating the nation's needs and its opportunities for greater efficiency through greater physical fitness.

June 9. They Shall Hear Again: A program devoted to the needs of the hard of hearing and indicating new opportunities for them through the use of hearing aids, lip reading, medical treatment and occasionally surgery. Guest speaker, Howard A. Carter, B.S. in M.E., Secretary of the American Medical Association Council on Physical Medicine.

June 16. Home Was Never Like This: A program devoted to the possibilities of the American health resort or spa in the treatment of disease. Guest speaker, Dr. Walter S. McClellan, chairman of the American Medical Association Committee on Health Resorts, speaking from New York.

June 23. Postwar Doctor: Problems in medical education and their influence on the public health. Guest speaker, Dr. Victor Johnson, Secretary of the American Medical Association Council on Medical Education and Hospitals.

When no speaker is announced the summary will be given by Dr. W. W. Bauer, Director of the Bureau of Health Education. Doctors Look Ahead is heard on one hundred and twenty-three stations of the National Broadcasting Company network each Saturday at 4 p. m. Eastern War Time (3 p. m. Central War Time, 2 p. m. Mountain War Time and 1 p. m. Pacific War Time). Beginning May 26 the program will be heard at 4:30 p. m. Eastern War Time and corresponding times in other time zone areas.

# Woman's Auxiliary

### New Jersey

A symposium on Postwar Problems of Community Health was recently sponsored by the Woman's Auxiliary to the Essex County Medical Society. Lieut. Col. Stuart Z. Hawkes, chief of Surgical Service, Army Air Force Convalescent Center at Mitchel Field, was guest speaker.

### Ohio

The Hamilton County auxiliary has had three forum meetings since October, the subjects being "Juvenile Delinquency," "Health in Our Schools" and "Global Medicine."

The Marion County auxiliary recently purchased a new incubator and bed oxygen unit for the City Hospital.

Members of the Chillicothe auxiliary were recently entertained by Miss Alice Myers, who gave a travel talk on Mexico City and Guatemala. The auxiliary has planned a bridge party and rummage sale to raise funds for purchasing an incubator for the Chillicothe Hospital.

The auxiliary to the Columbus Academy of Medicine sponsored a two part discussion, one devoted to "Health Examinations for School Children and Employees" and the second to the Kellogg school education plan. The superintendent of schools, several school nurses and the coordinator of school health projects took part in the discussion.

# Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

## ARKANSAS

**District Meeting.**—The First Councilor District Medical Society held its eighty-fifth semi-annual meeting at Jonesboro Country Club, May 15. The speakers were:

Dr. Allie C. Kolb, Little Rock, War Neurosis in Returning Soldiers.
Dr. Joseph F. Shuffield, Little Rock, Discussion of Medical Legislation.
J. P. Womack, Jonesboro, A Layman Looks at the Doctor.

## CALIFORNIA

**Veterans Studying Professions.**—Forty-one veterans were studying medicine, dentistry and pharmacy on the San Francisco campus of the University of California May 4, according to the university *Clip Sheet*. Thirty-eight of the veterans were registered under the G. I. Bill of Rights and three are under Public Law 16, which provides scholarships for veterans in need of rehabilitation. Ages vary from 20 to 44 years.

**Prevalence of Diphtheria.**—The report of 28 cases and 5 deaths from diphtheria in San Francisco for 1945 indicates an upward trend, according to Dr. Jacob C. Geiger, director of public health of the city and county of San Francisco. Of the 28 cases, 11 were from the military forces and had not been immunized. Ten were in adults ranging from 24 to 72 years, none of whom had ever been immunized. Of the 11 children affected 6 were newcomers to the community and had not been immunized. Of the 5 remaining children, 4 being newcomers, there was some history of immunization from one to fourteen years before the disease occurred in this group. Dr. Geiger points out that of these 5 none had ever been checked by the Schick test as to the efficiency of the immunization and no "booster" injections were given. There was no common source of the infection of these cases, except in one family, the source not having been traced up to May 7. There was no concentration of cases in any area or in any school. From 1941 to 1945 about 10 cases a year was the average, less than 1 a month, generally in adults with none of these immunized. Up to this year one could further consider the disease to be not one of childhood, Dr. Geiger stated.

## CONNECTICUT

**Student Members.**—One hundred and sixty-seven applications for membership as student members have been approved by the council of the Connecticut State Medical Society. This is the first time that the student members have been included as special members of the society, an action voted by the house of delegates (THE JOURNAL, Dec. 16, 1944, p. 1039).

## FLORIDA

**Changes in Health Officers.**—Dr. Frank V. Chappell, Tampa, has been appointed director of the Hillsborough County Health Department, succeeding Dr. Charles W. Pease, Tampa, who was named epidemiologist of the department.——Dr. Kolbein L. K. Waering, Jacksonville, director of the Duval County Department of Health, has resigned.——Dr. Smith L. Turner, Williston, has been named health officer of Levy County.——Dr. Joseph A. Markley, U. S. Public Health Service, has been appointed health officer of Duval County, succeeding Dr. Waering.

## ILLINOIS

**Changes in Status of Licensure.**—The Illinois Department of Registration and Education on March 6 took the following action:

Dr. Lawrence T. Browning, formerly of Holden, W. Va., license revoked for conviction of violation of the National Motor Vehicle Act.
Dr. Oscar F. Roberts, Chicago, license revoked for conviction of violation of Internal Revenue Code.
Dr. Toros Sarkisian, formerly of Denver, license revoked for conviction in the Colorado courts of performing an abortion.

**Personal.**—Dr. W. W. Bauer, Director of the Bureau of Health Education, American Medical Association, Chicago, will deliver a talk before the Citizens' Public Health Association of St. Clair County in Belleville, May 22, on "Health for All People."——Dr. Edward B. Miller has been appointed health officer for district number 2 including counties of Boone, Lake and McHenry, with headquarters in Woodstock. Dr. Miller, who was recently in the medical corps of the Army of the United States, succeeds Dr. Fred O. Tonney.

**New Society of Ophthalmology and Otolaryngology.**—The Central Illinois Society of Ophthalmology and Otolaryngology was recently formed for the benefit of those practicing in these specialties in the central part of Illinois. Officers include Drs. Watson Gailey, Bloomington, president; Walter D. Stevenson, Quincy, and Stuart Broadwell Jr., Springfield, vice president, and William F. Hubble Jr., Decatur, secretary-treasurer. The membership is limited to 50 and is open to members of the national board or those eligible to membership in it. Three meetings a year will be held, the first of which was in Bloomington, April 21-22.

### Chicago

**The Maurice Lamm Blatt Memorial Fund.**—Colleagues of the late Dr. Maurice Lamm Blatt on the pediatric staff of the Cook County Hospital are sponsoring the establishment of the Maurice Lamm Blatt Memorial Fund. Proceeds would be used to create either an annual prize for a resident or intern doing outstanding work in pediatrics or, if sufficient funds are forthcoming, a fellowship, scholarship or lectureship in pediatrics. Three categories have been designated for membership in the project: any amount up to $25, contributing membership; $25 or more, sustaining membership, and $100 or more, life membership. Checks should be made payable to Dr. Meyer A. Perlstein, chairman of the Maurice Lamm Blatt Memorial Fund, 185 North Wabash Avenue, Chicago 1.

**Personal.**—Dr. Herman L. Kretschmer, President of the American Medical Association, has been named chairman of a committee to raise funds to pay for transferring the 276 ton Louis Pasteur Memorial statute from Grant Park to the Medical Center district on the west side, newspapers reported May 14. Ray McCarthy, president of the Medical Center Commission, said title to the memorial has been conveyed by the Chicago Park District Board. The Pasteur Memorial, a 51 ton statue on a 225 ton base, stands on the west lawn of the Chicago Natural History Museum.——Dr. Max Thorek will deliver the commencement address of the Iowa Wesleyan College, Mount Pleasant, Iowa, May 27, on "Medicine in a Mad World." Dr. Thorek will receive on this occasion the honorary degree of doctor of science.

**Malcolm MacEachern Award.**—The Johnson and Johnson Research Foundation has created an annual award at Northwestern University consisting of a silver medal and an honorarium of $250 to be known as the Malcolm T. MacEachern Award. The award honors Dr. MacEachern, associate director of the American College of Surgeons and director of the program in hospital administration at the school. The award was announced at a National Hospital Day celebration in the auditorium of the American College of Surgeons, May 12, simultaneously with an announcement of a five year grant of $75,000 to the program in hospital administration, including scholarships, also from the Johnson and Johnson Research Foundation, to supplement $15,000 granted two years ago. A renewal of scholarship grants by the American Hospital Supply Corporation was also announced. Since the program in hospital administration was started in September 1943, 113 students coming from seventeen states have enrolled in one or more of the nine new courses offered, in addition to taking background courses in other departments of the university. An advisory committee, board of consultants and faculty consisting of authorities in the hospital field assist in formulating policies of the program, conduct the courses and demonstrations and supervise the internships required before conferring degrees. Dr. Irvin Abell, Louisville, Ky., chairman of the board of regents of the American College of Surgeons, spoke on "The Significance of National Hospital Day, 1945."

## KENTUCKY

**Past President Honored.**—Dr. John H. Blackburn, Bowling Green, was recently given a dinner in honor of his completion of forty-five years in the practice of medicine. Dr. Blackburn was councilor of the Kentucky State Medical Association from 1921 to 1928, when he was elected to the presidency.

**Distinguished Service Medal.**—The Kentucky State Medical Association is now accepting names for the distinguished service medal approved in 1944 to be awarded annually to one of its members. Any member of the association is eligible to be nominated by any other member as an applicant

for the medal. All names will be considered by the council of the association, three to be selected as being worthy and these three to be submitted to the house of delegates for final selection.

**Sigma Alpha Affiliates with Alpha Epsilon Delta.**—On April 29 Sigma Alpha, premedical fraternity of the University of Louisville, became affiliated with Alpha Epsilon Delta, national honorary premedical fraternity, on its installation as the Kentucky Alpha chapter. The initiation of eighteen active and three honorary members was conducted by Hugh E. Setterfield, Ph.D., associate professor of anatomy, Ohio State University, Columbus, and national president of the Alpha Epsilon Delta. Dr. Setterfield's subject at the banquet was "What Kind of Doctor?" Sigma Alpha was organized on March 29, 1933 at Louisville under the auspices of Alfred W. Homberger, Ph.D., professor and head of the department of chemistry and premedical adviser. Alpha Epsilon Delta was founded at the University of Alabama in 1926 and now includes thirty-four chapters.

**Personal.**—Dr. Percival Bailey, professor of neurology and neurologic surgery at the University of Illinois College of Medicine, was commonwealth visiting professor of neurology and neurologic surgery at the University of Louisville School of Medicine during the month of April.——James T. Lowe, Ph.D., has been appointed director of nutritional research for the Nestle's Milk Products, Inc., New York. Dr. Lowe has been research associate for the Wisconsin Alumni Research Foundation, Madison, Wis., for the past ten years.——Dr. Bohdan G. Giel, U. S. Public Health Service, has been temporarily assigned as health officer in Perry County.——Dr. William H. Smith was chosen president of the Boyle County Board of Health recently to succeed the late Dr. John D. Jackson, who had held the position for twenty-two years. Dr. Perry C. Sanders was elected secretary of the board and health officer of Boyle County for another two year term. He and Dr. Smith have also been members of the board for twenty-two years. All are of Danville.

## MICHIGAN

**County Society Creates Administration Plan.**—The Calhoun County Medical Society has elected an active policy committee to direct and coordinate the administrative program of the society. Dr. Joseph E. Rosenfeld, Battle Creek, as chairman of the committee, will be in charge of all publicity; Dr. George A. Zindler, Battle Creek, as secretary is in charge of coordinating all postgraduate and postwar educational problems in the local hospitals for returning military members, including the raising of funds for the committee program. Dr. Carl G. Wencke, Battle Creek, will have charge of political medicine. Dr. Russell L. Mustard, Battle Creek, will develop plans for a central office and executive secretary and a central telephone agency. Dr. Duward L. Finch, Battle Creek, will have charge of the rehabilitation problems of members returning from war service as well as the responsibility of keeping in communication with them, sending bulletins and other useful information. Dr. Alpheus T. Hafford, Albion, is to coordinate all the activities in the county areas outside of Battle Creek.

**Provision for Accident Care.**—Effective May 1, new certificates greatly broadening the protection of enrolled physicians and their office employees were issued by Michigan Hospital Service and Michigan Medical Service. The new certificates make the hospital service virtually all inclusive for the average case and extend the surgical plan in all respects, including the addition of a provision for accident care. Certificates will be provided at a moderate increase in rates for the hospital protection and at no increase in rates for the surgical protection. The benefits show an increase in the number of full days' service from twenty-one to thirty for patients, the provision of the same amount of care for every disability rather than a limitation of care by the year, and the addition of such former "extras" as basal metabolism examinations, accident room care, physical therapy, extensive laboratory service and penicillin. Recent changes in the surgical benefit contract of the Michigan Medical Service include a $150 maximum providing for full surgical service for those conditions requiring multiple stage operations, such as tuberculosis and cancer. In maternity benefits the waiting period will apply only to childbirth and is reduced from ten to nine months. Miscarriage, ectopic pregnancy and the like will be covered from inception of the contract, while the former exception to self-inflicted injuries has been eliminated. Emergency surgical service in the outpatient department of the hospital will be provided for accidental injuries but will not include outpatient x-ray service. In addition, a special rider contract provides pathologic laboratory services to all subscribers to Michigan Hospital Service.

## MINNESOTA

**Personal.**—On April 1 Dr. Donald W. Pollard, who has been absent from the superintendency of Minneapolis General Hospital because of war leave, was to return to the Minneapolis General Hospital, having been placed on inactive duty. Dr. Francis E. Harrington, formerly city health officer, has been acting superintendent since August 1942 (THE JOURNAL, Aug. 19, 1944, p. 1150).——Dr. Sidney A. Slater, superintendent of Southwestern Minnesota Sanatorium, Worthington, since 1919, will receive the honorary degree of doctor of science at the University of Richmond, Richmond, Va., April 27. He will be presented with a Phi Beta Kappa key which was previously awarded. Dr. Slater graduated at the University College of Medicine, Richmond, in 1909.

**Airlines Contribute to Mayo Fund.**—The Northwest Airlines gave $5,000 to the Mayo Memorial Fund recently as a tribute to the contributions of the Mayo Clinic to both wartime and peacetime aviation in pioneering scientific researches with especial attention to high altitude flying. The donation, voted by the company's board of directors, was accompanied by a resolution calling attention to the establishment by the state legislature of a research center at the University of Minnesota and emphasizing the "close collaboration of the Northwest Airlines with the Mayo Clinic for many years" (THE JOURNAL, January 13, p. 111). An announcement credits the work of the clinic before the war, in charge of Col. William R. Lovelace, M. C., now in charge of the Army Air Forces research center at Wright Field, Dayton, Ohio, and discusses the studies of the use of oxygen in high altitude flying in which the Northwest Airlines cooperated.

## NEBRASKA

**State Medical Election.**—Dr. Earle G. Johnson, Grand Island, was named president-elect of the Nebraska State Medical Association at a meeting of the house of delegates in Lincoln, May 8. Dr. Charles McMartin, Omaha, is president.

**Society News.**—The Omaha-Douglas County Medical Society was addressed May 8 by Mr. J. W. Holloway Jr., Director of the Bureau of Legal Medicine and Legislation of the American Medical Association, Chicago, on "Trends in Federal Legislation" and Dr. Victor E. Johnson, Secretary, Council on Medical Education and Hospitals, American Medical Association, on "Postwar Problems and Plans in Medical Education."

**National Broadcast Features Hospital Day.**—Dr. Donald C. Smelzer, Philadelphia, president of the American Hospital Association, gave a special talk May 13 at Creighton Memorial St. Joseph's Hospital, Omaha, which was delivered over one hundred and twenty-three stations as a National Hospital Day feature. The talk was a part of the program "Your America," sponsored by the Union Pacific Railroad. The program also included an interview over the radio of Dr. Adolph Sachs, Omaha, medical director of the Union Pacific Railroad, with Ray Olson, Omaha radio newscaster. The official celebration was observed May 12 but the Sunday broadcast was a part of the program.

## NEW YORK

**Retirements at Rochester University.**—John R. Murlin, Ph.D., professor of physiology and director of the department of vital economics, University of Rochester School of Medicine and Dentistry, Rochester, will retire July 1. Dr. Edwin Fauver will retire at the same time as head of the physical education department and college physician. Both men have been connected with the Rochester faculty for twenty-eight and twenty-nine years respectively.

**Civic Medal Goes to Dr. Kaiser.**—On May 3 the Rochester Museum Association presented to Dr. Albert D. Kaiser, recently appointed health officer of Rochester, the Rochester Civic Medal. John Edward Hoffmeister, Ph.D., Rochester, president of the museum association, cited Dr. Kaiser for "civic responsiveness, his standing as a physician, his professional interest in public health and his achievements in the fields of exploration, scholarship and leadership."

**County Society Opens New Headquarters.**—The Richmond County Medical Society recently opened a permanent office in the Medical Arts Building, 100 Central Avenue, St. George, Staten Island 1. While the society does not plan to

engage a full time executive secretary, an information bureau will be maintained giving service concerning medical conferences in the hospitals, civilian and military, and miscellaneous data. Mrs. R. Hefftner will continue the secretarial services of the society, a position she has held for the last five years.

**Physical Fitness Check-Up Week.**—The week of June 4-8 has been designated physical fitness check-up week for high school pupils in New York State. The observance was held last year for the first time. The program this year will include medical and dental examinations, follow-up services, health instruction and practice, and achievement in physical activities based on statewide standards that were issued last September. These standards were developed in cooperation with the Selective Service System and the Army and Navy and represent achievements in individual developments that will mean better physical fitness for boys and girls in both wartime and postwar living.

**Albert Fisher Honored.**—Dr. Albert K. Fisher, Ossining, was honored with a dinner at the Cosmos Club, Washington, D. C., recently to celebrate his eighty-ninth birthday. Dr. Fisher, who graduated at Columbia University College of Physicians and Surgeons, in 1879, left the practice of medicine to enter the field of natural history. In 1883 he helped found the American Ornithologists' Union. On July 1, 1885, he became associated with the U. S. Department of Agriculture when a unit was set up there to study the interrelation of birds and agriculture. Dr. Fisher was associated with the unit for forty-six years, was a member of the Death Valley Expedition of 1891, of the Harriman (Alaska) Expedition of 1889 and the Pinchot South Sea Expedition of 1929 and from 1902 to 1906 assistant chief of the U. S. Biological Survey, later serving as senior biologist in charge of the division of economic investigations, under which the field organization of cooperative predatory animal and rodent control was built up. In 1931 he was retired from the department and was given an honorary appointment as collaborator in biology in the U. S. National Museum.

## New York City

**Grants to Columbia.**—Columbia University recently announced $50,428 in gifts. The contributions for medical work include $15,000 from the Josiah Macy Jr. Foundation for research in the school of medicine and $8,000 from the Rockefeller Foundation for research in neuropathology.

**Alumni Meeting.**—The Alumni Association of the New York University College of Medicine is holding its ninth annual Alumni Day at the college, May 26. Dr. Donal Sheehan, acting dean, will review the college activities in the past year and discuss plans for the development of the new medical center, and Dr. George G. Deaver will discuss "Plans for the Development of the Baruch Division of Physical Medicine and Rehabilitation."

**The Medical Quarterly.**—The Alumni Association of the New York University College of Medicine has begun the regular publication of the *Medical Quarterly*. Dr. Arthur C. De Graff is editor and Dr. Hippolyte M. Wertheim is chairman of the publications committee. This is the first time the alumni association has attempted any such publication, the first issue of which appeared in April containing articles of general interest to the alumni regarding the school's history, its present activities and its plans for development, news items about the college and college organizations, and news and personals about individual alumni and members of the faculty.

**Personal.**—Dr. Nolan D. C. Lewis, medical director of the New York State Psychiatric Institute and Hospital, has been appointed editor of the *Journal of Nervous and Mental Disease* succeeding Dr. Smith Ely Jelliffe, Huletts Landing, who retired because of ill health.——Dr. John Mark Hiebert has been elected vice president of Sterling Drug, Inc., in charge of the Frederick Stearns and Company Division. Dr. Hiebert has been a member of the Sterling organization since 1934, advancing from the position of divisional vice president and general manager of the Stearns division, to which he was appointed when Stearns was acquired about a year ago (THE JOURNAL, June 17, 1944, p. 505).——Dr. Jacob Sobel has been appointed medical director of the Home and Hospital of the Daughters of Israel for the Aged.

**Welfare Council Opens Conference Service.**—On May 10 the Welfare Council of New York City announced the establishment on an experimental basis of a conference service for its 600 member agencies. The new service will be made available to the council's membership in eight broad functional groups: health services, family service and related case work services, child care, employment and vocational guidance, correctional and allied services, care of the aged, group work and recreation, and services for seamen. The purpose of the new service is "to facilitate the work of the council's standing committee on welfare and health services by establishing direct channels of communication between it and member agencies of the Welfare Council and by providing a means of exchanging information among agencies in functional groups." The conference service will operate experimentally for one year.

## PENNSYLVANIA

### Philadelphia

**New Auditorium at Woman's Medical College.**—On May 1 the Mary Dern Goodrich Auditorium was opened at the Woman's Medical College of Pennsylvania. The new section is named for the wife of Judge Herbert F. Goodrich, president of the college, who spoke at the official opening. The redecoration of the room and its equipment for motion picture and sound projection are the gifts of Mr. William Goldman. Dr. William G. Leaman Jr., professor of medicine at the medical college, showed the first and latest medical films taken at the college.

**The Ulrich Memorial Lecture.**—Dr. Roy E. Nicodemus, director of the department of obstetrics, George F. Geisinger Memorial Hospital, Danville, delivered the first George A. Ulrich Memorial Lecture, April 26, at Jefferson Medical College of Philadelphia. His subject was "The History of American Obstetrics." The lecture, which is named for Dr. George A. Ulrich, who died July 18, 1944, will be sponsored annually by the Epsilon charter of Alpha Kappa Kappa fraternity of Jefferson Medical College. Dr. Ulrich was clinical professor of obstetrics at Jefferson, where he graduated in 1901.

**Program on Health Education.**—On May 2 the Philadelphia Department of Public Health launched a concentrated year round educational campaign to improve the health of the citizens of Philadelphia. Attention is to be focused on pertinent facts concerning those diseases which constitute the greatest menace, and the medical schools, local professional groups and allied agencies are cooperating. A steering committee has been set up and the department of health will provide speakers and educational material, including sound motion picture films. The first program is devoted to tuberculosis and a slogan chosen to be used throughout the campaign is "Is There Tuberculosis in Your Home? Find Out!" Similar programs will be carried out for rheumatic heart disease, nutrition, child health, diabetes, cancer, venereal disease, labor, industry and industrial medicine, respiratory diseases, clubs, personal hygiene and mental hygiene.

## RHODE ISLAND

**Personal.**—Dr. John F. Kenney, Pawtucket, has been installed as president of the New England Conference of Industrial Physicians, succeeding Dr. Daniel L. Lynch, Boston. Dr. Thomas P. Kendrick, Boston, is the president-elect.

**Proposed Institute of Pathology.**—The establishment of a central Institute of Pathology to serve many or all of the hospitals in Rhode Island has been proposed by the committee on university, hospital and medical society relations of the Rhode Island Medical Society. It is recommended that the staff of the institute be large enough so that each hospital can have the personal attention of experts for frozen sections, conferences, staff meetings, tumor clinics, teaching of interns and residents and perhaps some lecturing to student nurses. It was also recommended that the work of all technologists be supervised by experts in bacteriology and biochemistry, the hospital technologists to be kept up to date by periodic review and training at the central laboratories of the proposed institute. Under the proposed setup a system of residency in pathology in preparation for national board certification would be an important part of the organization. Men qualifying for this work would receive a part of their training, third or fourth year, as resident pathologists in the larger of the participating hospitals. The institute would have a board of directors representing participating hospitals and a medical advisory committee consisting of one representative from each participating hospital. According to the outline of the plan, two or more technologists would fill in at hospitals while their regular technologists were at the institute for additional training and during vacations. Surgical specimens could be collected each day and examined at the institute, and pathologists would go out from the institute to the hospitals for frozen sections and necropsies. All serologic tests would be done at the institute, as would less common and more com-

plicated chemical and bacteriologic procedures. The proposal suggests that costs be shared by participating hospitals on the basis of the number of beds or other arrangements made by the board of directors. Each hospital would continue to charge its own patients for laboratory work according to its own plan.

## SOUTH CAROLINA

**Personal.** — Dr. Franklin L. Geiger, Columbia, assistant director of rural sanitation, state board of health, has been appointed medical director of a tuberculosis survey which is being carried on in South Carolina.——Walter L. Hard, Ph.D., assistant professor of histology, University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, has been appointed assistant professor of anatomy at the Medical College of the State of South Carolina, Charleston, *Science* reports.

**New President of State Society.**—At the executive meeting of the council of the South Carolina Medical Association in Columbia, April 17, Dr. William Thomas Brockman, Greenville, was installed as president. Dr. William R. Wallace, Chester, had asked to be relieved of his activities as president. The action of the council was over the protest of Dr. Brockman, who took the position, it is reported, that the constitution and by-laws provided that his installation should occur at the annual meeting of the association and that, if Dr. Wallace wished relief and resigned, the vice president should automatically assume the presidency.

## PUERTO RICO

**University News.** — Dr. Leland E. Hinsie, professor of psychiatry of the Columbia University College of Physicians and Surgeons, New York, gave a series of lectures on psychosomatic medicine at the School of Tropical Medicine in San Juan recently. Dr. Hinsie also addressed the Ponce District Medical Society on "The Person in the Body," the student body of the Polytechnic Institute at San Germán on "What Is Psychiatry?" and the students of social work at the University of Puerto Rico on "Psychosomatics in Social Work."

**Funds for New Construction.**—The legislative assembly of Puerto Rico recently passed bills for the construction of a new district charity hospital in Caguas to cost $1,500,000. This hospital is included in a six year financial plan of the government. Other legislation was passed appropriating $500,000 for expansion of the Psychiatric Hospital of Puerto Rico, Rio Piedras, and $500,000 for the Cancer Institute. Similar legislation provides for new additions to the Municipal Hospital at Trujillo Alto and one in Anasco. Plans allow for the construction of municipal hospitals in Naranjito, Corozal and Rincon.

## GENERAL

**International Surgical Assembly.**—The fifth International Assembly of the International College of Surgeons and tenth anniversary of its foundation in Geneva, Switzerland, will be celebrated at the invitation and under the auspices of the Peruvian government and the Peruvian chapter of the International College of Surgeons in Lima, Peru, September 10-12. Dr. Francisco Graña, head of the surgical department of the University of Lima, Peru, is general chairman. Additional details may be obtained from Dr. Max Thorek, general secretary of the college, 850 Irving Park Road, Chicago.

**Pan American Congress of Otolaryngology.**—The first Pan American Congress of Oto-Rhino-Laryngology and Broncho-Esophagology, to be sponsored by the American Academy of Ophthalmology and Otolaryngology, will take place October 12-13 at the Palmer House, Chicago, immediately following the 50th anniversary meeting of the academy. If transportation conditions permit, a representative attendance is expected from all of the Latin American countries. The academy committee has been in touch with the officers of the various Latin American otolaryngologic societies and through them has received assurance of fullest cooperation in this congress. Dr. Chevalier L. Jackson, Philadelphia, is chairman of the committee on Pan American Congress of Otolaryngology of the academy.

**Report of International Health Division.**—Chief activities of the health commission of the International Health Division of the Rockefeller Foundation in 1944 were louse control studies in Mexico, typhus and malarial control in Italy, malarial work in Egypt, the study of infective jaundice and other infectious diseases, nutrition studies in England and the manufacture and distribution of yellow fever vaccine. These projects were financed by $1,000,000 earmarked for this emergency work out of the total budget of $3,200,000 for the entire division. In 1944 attention was concentrated on twelve specific diseases, the most important of which were yellow fever, malaria, typhus, and the deficiencies related to nutrition. Perhaps the most significant contribution of the International Health Division to public health has been in the field of public health education. In 1944 fairly substantial sums were appropriated for fellowships and travel grants and for the support of schools of hygiene and public health nursing and to support nursing schools in Canada, Colombia, Brazil, Ecuador, Argentina, Venezuela and Portugal. According to the annual report, the division carried on operations in twenty-three different countries. In its research program the report of the division indicates that significant was the discovery of active virus of yellow fever in a sick monkey, a marmoset. The animal was seriously ill and soon died after it had been trapped in June 1944 by the laboratory at Ilhéus, Brazil. Exhaustive laboratory tests showed conclusively that it had died of yellow fever. The episode is historically interesting, the report points out, because it is the first time in any country that a wild animal has been picked up in its natural habitat suffering from yellow fever and holds support to the thesis that yellow fever is primarily a disease of jungle animals transmitted by "jungle mosquitoes."

**Services in Alcohol Hygiene.**—The National Committee on Alcohol Hygiene, Inc., Baltimore, announces the availability of a bimonthly publication, *Alcohol Hygiene*, to be used for educational purposes. The committee also announces the following services:

Scientific medical-worker speakers for lay and other seriously minded students of alcoholism.
A research staff to organize and sponsor institutes.
A clearing center for proper evaluation of published material by the scientific research committee and for distribution of acceptable reprints.
Consultation service for Community Chest and other groups to aid in the organization of medically and psychiatrically supervised alcoholic diagnostic and treatment clinics.
Material on fundamental preventive measures based on practical medical-psychiatric knowledge and experience, and on treatment of the individual who has an alcohol problem.

Dr. Robert V. Seliger, Baltimore, is executive director of the National Committee on Alcohol Hygiene and Robert M. Lindner, Ph.D., Lewisburg, Pa., director of educational and editorial projects. Dr. Lawrence F. Woolley, Baltimore, is director of clinical investigators, and Victoria Cranford is director of scientific investigators.

## CANADA

**The Jackson Memorial Lecture.**—Dr. Stanley Cobb, Bullard professor of neuropathology, Harvard Medical School, Boston, delivered the tenth annual Hughlings Jackson Memorial Lecture of the Montreal Neurological Institute, May 9, on "Some Observations on Neurocirculatory Asthenia." Following the address, a specially bound volume of the "Selected Writings of John Hughlings Jackson," edited by James Taylor, was presented to the lecturer.

**Changes in Health Personnel.**—John T. Phair, D.P.H., Toronto, chief medical officer of the Ontario Department of Health, has been appointed deputy minister of health to succeed the late Dr. Bernard T. McGhie. Dr. Aquila Lapierre, Outremont, Quebec, has been appointed director general of the administrative and technical services of the ministry of health and social welfare of the province of Quebec. He held the position from 1936 to 1939.

**Canadian Medical Meeting.** — The seventy-sixth annual session of the Canadian Medical Association will be held at the Mount Royal Hotel, Montreal, June 11-15, under the presidency of Dr. John Harris McPhedran, Toronto. The preliminary program includes the following speakers:

Dr. Gabriel Nadeau, Rutland, Mass., Obstetrics and Gynecology in New France.
Dr. Albert D. Ruedemann, Cleveland, Use of Beta Radium in Lesions of the Eye.
Dr. Alexander E. MacDonald, Toronto, New Treatment of Entropion.
Dr. Owen H. Wangensteen, Minneapolis, The Management of Bowel Obstruction.
Dr. Reginald P. Vivian, Port Hope, Ont., minister of health for Ontario, Role of Public Health in the Practice of Medicine.
Surg.-Lieut. Comdr. Donald S. Mitchell, Experiences of Penicillin in Dermatitis in the Forces.
Dr. Frederick A. Willius, Rochester, Minn., Critical Evaluation of Methods of Diagnosis in Cardiac Disease, with Special Reference to Electrocardiography.

Other groups meeting simultaneously will include the Canadian Orthopaedic Association, Canadian Association of Radiologists, Canadian Society for the Study of Diseases of Children, Federation of Medical Women of Canada, Canadian Medical Protective Association, Canadian Society for the Control of Cancer and Royal College of Physicians and Surgeons of Canada.

# Foreign Letters

## LONDON

*(From Our Regular Correspondent)*

April 21, 1945.

### The Physiologic Problem of Tickle Due to Wool Next the Skin

The director of research to the Wool Industries Association, Mr. B. H. Wilsdon, states in his annual report that a physiologic problem arises in the use of wool next the skin—that of tickle. This he describes as an idiosyncrasy for which no adequate explanation has been given. There is evidence that the reaction can be moderated when wool is given chemical treatment, such as that afforded by papain, which reduces the scaliness of the fiber. But he avoided claiming that this treatment produces "nontickle fiber." He believed that certain sensitive subjects may still react. The type of reaction may be quite dissimilar in different cases. The possibility must not be disregarded that some degree of tickle may be of hygienic value in stimulating the skin and controlling the peripheral circulation.

### Consultants and the Proposed National Health Service

Two meetings of London consultants—one for those attached to hospitals south of the Thames and the other for those attached to hospitals north of the Thames—were called by the British Medical Association and the Royal Colleges to discuss the government's proposals for a national health service. Lord Moran, president of the Royal College of Physicians, who presided at the former meeting, urged that any central health services council should have real powers and not be a reproduction of many old advisory bodies with purely negative functions. Even more important was it that power should be given to the regional councils—expert bodies which would have to deal with local authorities. A committee of ninety-three representative of the Royal Colleges, the British Medical Association, the teaching hospitals and the universities had unanimously urged that these councils should be planning bodies, with advisory powers over finance. The crux of the whole problem was the medical profession's fear of interference by local authorities in clinical work. If the regions were based on university centers and the planning was done from these in such a manner as to afford consultants a voice, they would not be at the mercy of local bodies. As far as negotiations with the government had proceeded, any substantial concessions gained had been in the field of general practice, not in that of consultant or specialist practice.

Sir Alfred Webb-Johnson, president of the Royal College of Surgeons, who presided at the other meeting, concurred in Lord Moran's view as to the need for investing the regional councils with real powers. Among matters which he hoped would still be pressed on the government were the separation of the medical service from the general social insurance, the introduction of the service by stages (the development of the hospital system coming first) and the bringing together of all health services under the Ministry of Health. In closing the meeting he said that he thought we were getting near to an administrative structure which would be acceptable to the profession.

### Sir Thomas Lewis

The death of Sir Thomas Lewis at the age of 64 has removed from British medicine a great investigator of disease. The method which he made his own and never tired of advocating he termed "clinical science," the main innovation being to bring the methods of the laboratory to the bedside. He condemned the usual separation of clinical and laboratory work into the hands of different persons. The clinician should perform both. He regarded the chief weapon of medicine to be the experimental method directly applied to man. His most important work was done on diseases of the heart. He was turned in this direction by the influence of Mackenzie, the leading cardiologist of the day, a position to which Lewis succeeded. Mackenzie was deeply interested in the mechanism of persistent cardiac irregularity, which his polygraphic studies led him to attribute to "nodal rhythm"; but the introduction of Einthoven's string galvanometer enabled Lewis (simultaneously with two Austrian workers) to show that the cause was auricular fibrillation. The discovery of auricular flutter followed. Experience in the war of 1914-1918 led to investigation of soldier's heart, which he embodied in the book "The Soldier's Heart and the Effort Syndrome." Other works, all of which became standard, were "Mechanism and Graphic Registration of the Heart Beat," "Clinical Disorders of the Heart Beat" and "The Blood Vessels of the Human Skin and Their Responses." He investigated dermatographia and produced evidence for the independent contractility of the capillaries. He described "a triple response" of the tissues of the skin to injury, due to release from the injured cells of a histamine-like substance. Experimental and clinical studies were embodied in a remarkable book entitled "Pain," in which he showed that pain arising from the skin was of a different kind from pain arising deeply. He showed the intervention of chemical agents in the production of cutaneous pain and tenderness. He attributed the latter to axon reflexes through fibers not previously known, which he termed "nocifensor." He also showed the segmental distribution of pain arising from deep structures. His work received early recognition in the United States. In 1914, at the early age of 33, he delivered the Herter lectures at Baltimore and a Harvey lecture in New York. For a period he was visiting physician attached to the Peter Bent Brigham Hospital, Boston. All his advances were made by the experimental investigation of disease in man, which he was always strenuously advocating. He was editor of two journals devoted to research: *Heart* from its foundation in 1908 and its successor *Clinical Science* until last year.

### German Ill Treatment of British Prisoners of War

Plans are completed for the reception in this country of 160,000 liberated British prisoners of war. Camps are being prepared for them at coastal resorts with staffs of doctors, specialists and welfare officers. Many men will require building up after the malnutrition and ill treatment endured in German prison camps. Every man will receive the usual forty-two days' leave and double rations. A report from Hanover describes 100 prisoners too ill to move. Among them were 32 who had survived a grueling march of 500 miles across Germany to prevent their liberation by the approaching Allied army.

# Marriages

FRANCIS LEO DENZER, Brooklyn, to Miss Marie Loretta Mooney at Flushing, N. Y., May 8.

WILLIAM CLARKE QUINN, Crisfield, Md., to Miss Jean Quinn of Statesville, N. C., March 31.

JOHN B. BLALOCK to Miss Margaret Ashe Tutwiler, both of Birmingham, Ala., April 14.

EDWARD M. POSER, Columbus, Wis., to Miss Elizabeth Ann Shearer of Edgerton recently.

HAL E. BENNETT, Troy, Tenn., to Miss Joan Ottilee Tabor of Belvidere, Ill., April 11.

LAWRENCE V. LITTIG, Madison, Wis., to Miss Sally Margaret Ebert, Cuba City, recently.

WILLIAM BROWN to Dr. Elizabeth L. Brown, both of New York, April 12.

HARRY A. SHEARER to Miss Violet Lundt, both of Beloit, Wis., recently.

# Deaths

**Walter Gray Crump Sr.,** ⊕ New York; New York Homeopathic Medical College and Hospital, New York, 1895; emeritus professor of surgery at his alma mater, now known as the New York Medical College, Flower and Fifth Avenue Hospitals; served as professor of surgery at the New York Polyclinic Medical School and Hospital and as professor of gynecology at the New York Medical College and Hospital for Women; member of the Academy of Pathological Science; member of the board of governors and fellow of the American College of Surgeons; director of the National Association for the Advancement of Colored People; a founder of the Broad Street Hospital, where he had been medical director and attending surgeon; a founder of the Beekman Street Hospital; consulting surgeon, Evangelical Deaconess and Prospect Heights hospitals, Brooklyn, Yonkers (N. Y.) General Hospital, Southside Hospital, Bay Shore, N. Y., Mount Vernon (N. Y.) Hospital, Dobbs Ferry (N. Y.) Hospital, Fitkin Memorial Hospital, Neptune, N. J., and the Flower and Fifth Avenue Hospitals; consulting gynecologist at the United Hospital in Port Chester, N. Y.; trustee, Howard University in Washington, D. C., and the Tuskegee Institute in Alabama; in 1934 received the honorary degree of doctor of science from the Albright College in Reading, Pa.; died in the Flower and Fifth Avenue Hospitals May 1, aged 75.

**Charles Morgan McKenna** ⊕ Chicago; Rush Medical College, Chicago, 1905; professor and head of the division of urology in the department of surgery at the University of Illinois College of Medicine which he had joined in 1913 as instructor in senior surgery; specialist certified by the American Board of Urology, Inc.; member of the American Association of Genito-Urinary Surgeons and the Institute of Medicine of Chicago; member and in 1922-1923 president of the Chicago Urological Society; member of the American Urological Association and past president of the North Central Branch; fellow of the American College of Surgeons; a captain in the medical corps of the U. S. Army during World War I; head of genitourinary surgery at the Research and Educational Hospitals and St. Joseph Hospital; attending urologist at the Norwegian-American Hospital; attending urologist at the Cook County Hospital from 1927 to 1938; contributed a chapter on "Tuberculosis of the Urogenital Tract" in Clinical Tuberculosis by Dr. Benjamin Goldberg; died May 13, aged 65, of coronary occlusion.

**Henry W. Grady Shytles,** Abilene, Texas; University of Tennessee College of Medicine, Memphis, 1914; president of the Taylor County Medical Society in 1930 and of the Scurry-Dickens-Kent-Garza-Borden-King-Stonewall Counties Medical Society from 1939 to 1943; member of the American Medical Association; during World War I associated with the U. S. Public Health Service, inspecting army camps throughout the country; for three years physician and surgeon for the Pima Indian reservation in Arizona; while residing at Snyder, Texas, served as chairman of the Procurement and Assignment Advisory Committee for that area; formerly medical superintendent and chief surgeon of the Snyder (Texas) General Hospital; at one time assistant city physician in Fort Worth; a captain in the medical corps, Army of the United States, from April 1943 to August 1943, when he was honorably discharged because of his physical condition; on the staffs of St. Ann and the Hendrick Memorial hospitals; died Nov. 16, 1944, aged 53, of coronary thrombosis.

**James Thomas Wayson** ⊕ Honolulu, Hawaii; University of California Medical School, San Francisco, 1891; surgeon in the U. S. Cutter Service from 1892 to 1895; member of the House of Delegates of the American Medical Association in 1905; served as assistant administrator and member of the board of health of Hawaii; city and county physician of Honolulu from 1911 to 1918 and general health officer of Hawaii from 1918 to 1931; in 1932 was instrumental in setting up a separate board of hospitals and settlement to administer the leprosy phase of public health; held the position of board physician from the time of its inception until his retirement in 1943; served as chairman of the Hawaii Territorial Medical Examiners; member of the American Academy of Dermatology and Syphilology; at one time physician in charge of the Kaiihi Boys' Home and superintendent of the Kapiolani Girls' Home; died January 11, aged 74.

**Archibald Henry Busby,** New Canaan, Conn.; Columbia University College of Physicians and Surgeons, New York, 1898; decorated for gallantry in the Battle of San Juan Hill during the Spanish-American War; served in France with the New York Hospital Unit, Base Hospital number nine during World War I; fellow of the New York Academy of Medicine; charter member of the New York Roentgen Society; for many years head of the radiology department of the New York Hospital in New York, where since 1932 he had been consulting radiologist; at various times on the staffs of the Babies Hospital, French Hospital and St. Mary's Hospital for Children, all in New York; died April 25, aged 69, of heart disease.

**James Herbert Lawson,** New York; Columbia University College of Physicians and Surgeons, New York, 1902; one of the early officers of the medical reserve corps of the army, receiving his commission from President Taft in 1912; was with the American troops on the Mexican border in 1916; received a decoration from the French government for service during World War I; served at St. Vincent's and Lying-In hospitals; formerly attending surgeon at the Memorial Hospital and had been chief surgeon of the outpatient department at the Babies Hospital and of St. Mary's Hospital for Children; surgeon for many American Olympic teams; died April 25, aged 69, of coronary arteriosclerosis.

**Edmond Henri Sauvignet** ⊕ Laredo, Texas; Medical Department of Tulane University of Louisiana, New Orleans, 1898; formerly secretary and president of the Webb-Zapata-Jim Hogg Counties Medical Society; served as health officer of Webb County and of the city of Laredo; a charter member of the International Congress on Tuberculosis; examining physician for Webb County Draft Board during World Wars I and II; first resident physician and surgeon at the Santa Rosa Hospital in San Antonio from 1898 to 1900; on the staff of Mercy Hospital; district surgeon for the Missouri Pacific Railroad from 1901 to 1945; died January 27, aged 70, of uremia.

**Rebekah Wright,** Brookline, Mass.; Northwestern University Woman's Medical College, Chicago, 1896; member of the American Medical Association, American Psychiatric Association and the New England Society of Psychiatry; for many years associated with the Massachusetts State Department for Mental Diseases as a consultant in hydrology for all of the state's hospitals for mental and nervous diseases; since February 1, 1945 consulting hydrologist at the Connecticut State Hospital in Middletown, Conn., where she died March 29, aged 72, of arteriosclerotic myocarditis.

**Charles Berger Campbell** ⊕ Washington, D. C.; Georgetown University School of Medicine, Washington, 1894; also a pharmacist; major, medical corps, U. S. Army, not on active duty; served as chairman of the public health committee of the Federation of Citizens Associations of the District of Columbia and its delegate from the Medical Society of the District of Columbia; in 1944 was awarded the Evening Star Trophy for outstanding civic work; died in the Emergency Hospital February 5, aged 74, of uremia, hypertrophy of the prostate and pneumonia.

**John George Abele,** Portland, Ore.; University of Oregon Medical School, Portland, 1907; formerly city epidemiologist and city health officer; served during World War I; died in the Veterans Administration Facility, Roseburg, March 14, aged 74.

**Homer C. Ballard,** Lakewood, Ohio; Western Reserve University Medical Department, Cleveland, 1896; formerly on the staffs of the Lutheran and St. John's Hospital in Cleveland; on the staff of the Lakewood Hospital, where he died March 27, aged 77.

**George Louis Bartruff,** Brooklyn; Long Island College Hospital, Brooklyn, 1893; died March 10, aged 77.

**Ira Floyd Bean,** Melbourne, Fla.; Atlanta College of Physicians and Surgeons, 1912; member of the American Medical Association; died in a hospital at Jacksonville February 18, aged 59.

**Theophilus Henry Boysen** ⊕ Egg Harbor City, N. J.; Jefferson Medical College of Philadelphia, 1905; also a pharmacist; past president of the Medical Society of Atlantic County; served as medical examiner in the public schools, as a member of the board of health and at one time as councilman; died in the Jefferson Hospital, Philadelphia, March 30, aged 63.

**Benjamin Harrison Breakstone,** Chicago; Rush Medical College, Chicago, 1899; member of the American Medical Association; formerly professor of surgery at the Bennett Medical College; attending surgeon at the Cook County Hospital from 1902 to 1908; served on the staffs of the Mary Thompson Hospital for Women and Children, the People's Hospital and various other hospitals in Chicago; died April 23, aged 68.

**William Lewis Colquhoun MacBeth,** El Monte, Calif.; University of Toronto Faculty of Medicine, Toronto, Ont., Canada, 1909; member of the American Medical Association; died March 1, aged 58.

**William Henry Dale,** Eugene, Ore.; Rush Medical College, Chicago, 1904; member of the American Medical Association; past president of the Central Willamette Medical Society; served as a member of the board of health; at one time medical superintendent of the Harrisburg Private Hospital in Harrisburg; died March 14, aged 66.

**James Francis Dennis** ✠ Waterloo, Wis.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1908; died March 29, aged 62, of carcinoma of the sigmoid.

**Albert Powell Donoho,** Merchantville, N. J.; Medico-Chirurgical College of Philadelphia, 1900; served during World War I; died in the Temple University Hospital, Philadelphia, February 16, aged 69.

**Louis Warner Flanders** ✠ Dover, N. H.; University of Vermont College of Medicine, Burlington, 1885; past president of the New Hampshire Medical Society; honorary member of the Strafford County Medical Society; died January 16, aged 80.

**Edward Richard Gookin** ✠ Washington, D. C.; Baltimore Medical College, 1906; served overseas during World War I; formerly clinical instructor in ophthalmology at the George Washington University School of Medicine and assistant and later instructor in clinical ophthalmology at the Georgetown University School of Medicine; died March 6, aged 62, of coronary occlusion.

**Daniel Wesley Gray,** Searcy, Ark.; Memphis (Tenn.) Hospital Medical College, 1908; died suddenly February 5, aged 65.

**Forest Jackson Green,** Mineola, Texas; Dallas Medical College, 1903; member of the American Medical Association; examining physician and member of a draft board during World War I; died January 11, aged 66, of coronary occlusion.

**Thaxton Richardson Guill** ✠ Donelson, Tenn.; University of Nashville Medical Department, 1900; served as director of the Bank of Donelson; died March 22, aged 67, of heart disease.

**William Dandridge Haden** ✠ Charlottesville, Va.; University of Virginia Department of Medicine, Charlottesville, 1910; served three terms as mayor and twelve consecutive years as a member of the city council; member of the board of visitors of the University of Virginia; president of the National Bank and Trust Company; died in the University Hospital April 8, aged 60.

**James Thomson Hardy** ✠ Brooklyn; New York Homeopathic Medical College and Hospital, New York, 1900; veteran of the Spanish-American War; on the staffs of the Bushwick, Lutheran and Wade hospitals; died in the Nassau Hospital, Mineola, March 10, aged 68, of arteriosclerotic heart disease, auricular fibrillation and hypertrophy of the prostate.

**Richard Henry Harris,** Elkins Park, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1898; member of the American Medical Association; on the staff of the Abington Memorial Hospital, Abington, where he died March 29, aged 75, of cardiac insufficiency and cerebral thrombosis.

**Victor Hugo Hasek,** Cedar Rapids, Iowa; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1916; member of the American Medical Association; city physician and health officer; served during World War I; on the staffs of the Mercy and St. Luke's hospitals; died February 25, aged 53, of cerebral embolism of the left middle cerebral artery.

**Walton Hewetson,** Groveport, Ohio; Columbus Medical College, 1888; died February 18, aged 78.

**Edwin Carlton Higgins,** Manchester, Conn.; Tufts College Medical School, Boston, 1925; member of the American Medical Association; interned at St. Francis and Hartford Isolation hospitals in Hartford; on the staff of the Manchester Memorial Hospital; died March 31, aged 47, of coronary occlusion.

**Bayard Holmes,** Chicago; Rush Medical College, Chicago, 1904; on the consulting staff of the Illinois Masonic Hospital; on the courtesy staffs of St. Luke's and Henrotin hospitals; life member of the Art Institute of Chicago; died March 13, aged 65, of congestive heart disease and angina pectoris.

**John Howorth** ✠ Wilkes-Barre, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1909; fellow of the American College of Surgeons; past president of the Luzerne County Medical Society; served on the medical advisory board during World Wars I and II as well as on the surgical staff of the local induction center during the present war; chief of staff, Wilkes-Barre General Hospital; surgeon for the Lehigh Valley Railroad; died March 24, aged 65, of myocarditis.

**Marion Mercer Hursh,** Grand Rapids, Minn.; Minneapolis College of Physicians and Surgeons, medical department of Hamline University, 1908; served on the staff of the Itasca County Hospital; died January 20, aged 67.

**Harvey Green Johnston,** Pearisburg, Va.; University College of Medicine, Richmond, 1899; served as county medical examiner for the Selective Service during World Wars I and II; died March 21, aged 66.

**Moses Randolph Kahn,** Baltimore; University of Maryland School of Medicine, Baltimore, 1912; member of the American Medical Association; clinical professor of ophthalmology at his alma mater; formerly instructor of clinical ophthalmology at the Johns Hopkins University School of Medicine; served during World War I; at various times on the staffs of the Baltimore Eye, Ear and Throat Charity Hospital, Home for Incurables, Sinai Hospital and the U. S. Veterans Bureau; died January 11, aged 57.

**James William Kautz,** Cincinnati; Cincinnati College of Medicine and Surgery, 1890; died March 8, aged 80, of lobar pneumonia and grip.

**Theodore Wilbert Kemmerer,** Jackson, Miss.; State University of Iowa College of Medicine, Iowa City, 1901; for many years director of the state hygienic laboratory; at one time adjunct professor of clinical laboratory diagnosis at the University of Mississippi School of Medicine; formerly associated with the hygienic laboratory of the U. S. Public Health Service in Washington, D. C.; veteran of the Spanish-American War and World War I; died April 5, aged 67, of edema of the lungs and auricular fibrillation.

**Albert Koehler,** Baker, Ore.; Schlesische-Friedrich-Wilhelms-Universität Medizinische Fakultät, Breslau, Prussia, Germany, 1877; member of the American Medical Association; died March 1, aged 98.

**Werner Adolph Reinhold Lagus,** Warrenton, Ore.; Helsingfors Universitet Medicinska Fakulteten, Helsingfors, Finland, 1896; died in a hospital at Astoria March 19, aged 79, of coronary occlusion.

**Francis James Lawler** ✠ Carthage, N. Y.; Albany Medical College, Albany, 1916; health officer; served overseas during World War I; died in the Syracuse Memorial Hospital, Syracuse, March 23, aged 53, of myelogenous leukemia.

**Oscar Leslie Long,** Portland, Maine; Baltimore Medical College, 1898; for many years member of the city health department in Baltimore; died March 9, aged 71, of pulmonary edema, cerebral hemorrhage and arteriosclerosis.

**William F. MacLennan,** Gloucester City, N. J.; Medico-Chirurgical College of Philadelphia, 1896; also a pharmacist; died in Trenton March 24, aged 76.

**Clib B. May,** Little Rock, Ark.; University of Louisville Medical Department, Louisville, Ky., 1914; member of the American Medical Association; died February 23, aged 64.

**Luster Clark McCutcheon,** Green Bank, W. Va.; Chattanooga (Tenn.) Medical College, 1910; served a term as mayor of Richwood; died April 26, aged 61.

**Robert Davis McKinney,** Troy, N. Y.; Chicago Homeopathic Medical College, 1894; died January 3, aged 75, of carcinoma of the head of the pancreas.

**Allan McLean,** Morganton, N. C.; University of Maryland School of Medicine, Baltimore, 1908; member of the American Medical Association; for many years on the staff of the State Hospital; died February 22, aged 60.

**Jason E. Montgomery,** Weslaco, Texas; Baylor University College of Medicine, Dallas, 1908; member of the American Medical Association; local surgeon for the Missouri Pacific Railway; died suddenly January 30, aged 73.

**Carl G. Muehlmann,** Pekin, Ill.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1900; also a pharmacist; for twenty years a surgeon for the Illinois Central Railroad; surgeon for the Pekin Terminal Railroad; for many years served on the U. S. Pension Board; until the time of his death examining physician for U. S. Civil Service applicants; health officer of Pekin; died in the Pekin Public Hospital March 13, aged 80.

**Arthur Lapham Murray,** Washington, D. C.; George Washington University School of Medicine, Washington, D. C., 1904; served during World War I; for many years medical adviser in the Bureau of Mines, Department of the Interior; died February 28, aged 63.

**James Ball Naylor,** Malta, Ohio; Starling Medical College, Columbus, 1886; at one time health commissioner of Morgan County; author of many books; died April 1, aged 84, of heart disease.

**Herman J. Neubauer** ✠ Hinckley, Ill.; Chicago College of Medicine and Surgery, 1917; on the staffs of the DeKalb Public Hospital and St. Mary's Hospital in DeKalb, where he died March 23, aged 51, of fractured ribs received when he accidentally fell beneath the wheels of a farm machine on his farm.

**William Peter Rice,** Rhinelander, Wis.; Chicago College of Medicine and Surgery, 1915; died February 6, aged 63, of coronary occlusion.

**Charles Orean Rickenbrode** ✠ Farrell, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1908; died February 10, aged 60.

**Ivan Webster Riggins,** Indianapolis; Kentucky University Medical Department, Louisville, 1906; University of Louisville Medical Department, 1907; medical examiner for the Indianapolis Life Insurance Company and Acacia Mutual Life Insurance Company; on the staffs of the City Hospital, St. Vincent's Hospital and the Methodist Hospital, where he died March 15, aged 71, of coronary occlusion.

**William Ernest Risque,** Midway, Ky.; University of Louisville Medical Department, Louisville, 1893; past president of the Midland Medical Society; died March 9, aged 85, of coronary sclerosis.

**William Penn Roberts,** Sioux Falls, S. D.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1894; honorary member of the South Dakota State Medical Association; member of the American Medical Association, died January 12, aged 75.

**Thomas Peter Rothnem,** Fargo, N. D.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1912; specialist certified by the American Board of Radiology, Inc.; member of the Radiological Society of North America, Inc.; on the staffs of St. Luke's Hospital and Fargo Clinic; died January 19, aged 61.

**Daniel Ralph Russell,** Kansas City, Mo.; University Medical College of Kansas City, 1908; member of the American Medical Association; died March 22, aged 64.

**Ord Ledyard Sands,** Binghamton, N. Y.; University and Bellevue Hospital Medical College, New York, 1911; member of the American Medical Association; died January 23, aged 73, of coronary occlusion.

**Eugene Schumaker,** Rensselaer, Ind.; Rush Medical College, Chicago, 1934; interned at St. Joseph Hospital in Chicago; on the staff of the Jasper County Hospital; died March 12, aged 38, of coronary occlusion.

**Charles Young Seagle** ✠ Bertrandville, La.; Medical Department of Tulane University of Louisiana, New Orleans, 1904; died January 29, aged 67.

**Sam L. Segraves,** Era, Texas; Vanderbilt University School of Medicine, Nashville, Tenn., 1889; died February 21, aged 91, of general senility.

**Ebert T. Simpson,** Butler, Pa.; Western Pennsylvania Medical College, Pittsburgh, 1908; member of the American Medical Association; died January 2, aged 63, of coronary embolism.

**Clyde Leroy Smith** ✠ Fremont, Ohio; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1904; past president of the Sandusky County Medical Society; since 1940 city health commissioner and registrar; on the staff of the Memorial Hospital; died February 28, aged 66, of coronary occlusion.

**Dorland Smith** ✠ Bridgeport, Conn.; Yale University Medical School, New Haven, 1899; specialist certified by the American Board of Ophthalmology and the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology, American Ophthalmological Society and the Association for Research in Ophthalmology, Inc.; fellow of the American College of Surgeons; on the staff of the Bridgeport Hospital; died February 5, aged 69, of carcinoma of the pancreas with metastases to the liver.

**William Curtis Smith,** Scottsville, N. Y.; University of the City of New York Medical Department, New York, 1881; member of the American Medical Association; for many years St. Lawrence County coroner and supervisor of the town of Stockholm, where he was also health officer; served as director of the First National Bank of Winthrop from its inception in 1916 until his resignation in 1942; died March 2, aged 87, of lobar pneumonia.

**Fred Clifford Soper,** Dilworth, Minn.; State University of Iowa College of Medicine, Iowa City, 1905; coroner of Clay County; on the staff of the St. Ansgar Hospital in Moorhead; died in St. John's Hospital, Fargo, N. D., February 7, aged 63, of pneumonia.

**Albert A. Sprague,** Silverton, Ohio; Medical College of Ohio, Cincinnati, 1898; for many years secretary of the Silverton Building and Loan Company; died February 19, aged 82.

**Neile Spooner Storer** ✠ Republic, Ohio; Northwestern University Medical School, Chicago, 1906; served as mayor of Republic; on the staff of the Mercy Hospital in Tiffin; died February 28, aged 61, of coronary thrombosis.

**Ernest Bernard Studer,** Los Angeles; St. Louis Medical College, 1890; University of Pennsylvania Department of Medicine, Philadelphia, 1891; served on the staff of St. Vincent's Hospital; died March 19, aged 78, of cerebral hemorrhage.

**Gustave Herman Taubles** ✠ Carmel, Calif.; Cooper Medical College, San Francisco, 1908; served as chairman of the Carmel chapter of the American Red Cross; died January 24, aged 64.

**John Allen Thomson,** Sioux City, Iowa; Sioux City College of Medicine, 1904; member of the American Medical Association; formerly a member of the county board of health; member of the Selective Service Board number 2; died February 28, aged 65, of cerebral hemorrhage.

**Clarence Scott Trimble** ✠ Emporia, Kan.; Keokuk (Iowa) Medical College, College of Physicians and Surgeons, 1902; member of the American Academy of Ophthalmology and Otolaryngology and the Kansas City Eye, Ear, Nose and Throat Society; served during World War I; at one time health officer of Buckeye, Iowa; on the staffs of the Newman Memorial and St. Mary's hospitals; ophthalmologist for the Santa Fe Railroad for twenty-two years; died March 16, aged 67, of carcinoma of the stomach.

**Joseph C. Tufford,** San Diego, Calif.; Detroit College of Medicine, 1894; died February 16, aged 77, of uremia.

**Urania Tyrrel,** Philadelphia; New York Medical College and Hospital for Women, New York, 1890; died in the Hahnemann Hospital January 29, aged 77, of arteriosclerosis and coronary artery insufficiency.

**Thomas Mervelle Watson** ✠ Greenville, N. C.; Tulane University of Louisiana School of Medicine, New Orleans, 1919; specialist certified by the American Board of Pediatrics, Inc.; member of the American Academy of Pediatrics; formerly vice president of the North Carolina Pediatric Society; served during World War I; interned at St. Vincent's Hospital in Birmingham, Ala., and St. Louis Children's Hospital in St. Louis; on the staff of the Pitt General Hospital; died March 12, aged 50, of coronary thrombosis.

**Morris Weissberg** ✠ Brooklyn; Long Island College Hospital, Brooklyn, 1914; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; served in France during World War I; consulting physician at St. Luke's Hospital in Newburgh and at the Bushwick and Evangelical Deaconess hospitals; died March 17, aged 58, of coronary occlusion.

**John Westall,** Fall River, Mass.; Dartmouth Medical School, Hanover, N. H., 1892; served as president of the board of aldermen and a member of the board of health; died in the Truesdale Hospital, March 15, aged 83, of pyelonephritis and hypertrophy of the prostate.

**Furman Chairs Whitaker,** Bradenton, Fla.; the Hahnemann Medical College and Hospital, Chicago, 1895; died in the Tampa Municipal Hospital, Tampa, March 8, aged 88, of injuries received in a fall.

**Reuben H. Wood,** Stockton, Ill.; the Hahnemann Medical College and Hospital, Chicago, 1896; on the staffs of the Deaconess and St. Francis hospital in Freeport; died March 2, aged 85, of angina pectoris.

**Henry Wilson Wooden,** Orlando, Fla.; University of West Tennessee College of Medicine and Surgery, Memphis, 1914; Meharry Medical College, Nashville, 1916; died February 12, aged 53, of injuries received in an automobile accident.

**Sarah Delia Wyckoff** ✠ Kingston, Pa.; Johns Hopkins University School of Medicine, Baltimore, 1899; died in the Wilkes-Barre General Hospital, Wilkes-Barre, Pa., March 19, aged 72, of acute cardiac failure and ruptured appendix.

**George W. Young,** Pennington Gap, Va.; Hospital College of Medicine, Louisville, Ky., 1898; died March 2, aged 70, of hypertensive heart disease.

# DIED WHILE IN MILITARY SERVICE

**Arthur Eynon Beddoe** ✠ Surgeon, Lieutenant Commander, U. S. Navy, retired, San Diego, Calif.; University of Pennsylvania Department of Medicine, Philadelphia, 1910; entered the medical corps of the U. S. Navy as a lieutenant (jg) on May 21, 1914; retired on May 1, 1937 for incapacity resulting from an incident of the service; returned to active duty; promoted to the temporary rank of commander on Jan. 3, 1942; died July 18, 1944, aged 59.

**James Russell Bell** ✠ Canonsburg, Pa.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1932; interned at the Mercy Hospital in Pittsburgh; began active duty as a captain in the medical corps, Army of the United States, on June 5, 1942; later promoted to major; died near Prestwick, Scotland, in an aircraft crash in routine flight, Dec. 10, 1944, aged 40.

**John Birge Byers,** Grand Rapids, Mich.; Northwestern University Medical School, Chicago, 1941; interned at St. Luke's Hospital in Chicago; formerly a fellow in medicine in the Mayo Foundation, Rochester, Minn.; began active duty as a first lieutenant in the medical corps, Army of the United States, on June 6, 1942; later promoted to captain; a flight surgeon attached to an aircraft group in England, where he died Dec. 20, 1944, aged 32, of acute hemorrhagic pancreatitis.

**Richmond Cranston Holcomb** ✠ Medical Director, Captain, U. S. Navy, retired, Upper Darby, Pa.; Long Island College Hospital, Brooklyn, 1896; entered the navy in December 1898 with the rank of lieutenant (jg); while in Culebra, Virgin Islands, carried on special investigations in connection with intestinal parasites, especially schistosomiasis; the fluke was shown to be a distinct species, leading Sambon to naming it Schistosomum mansoni; assistant to the Bureau of Medicine and Surgery, Navy Department, Washington, D. C., from April 1914, until April 1918; was medical officer in command of the U. S. Naval Hospital, League Island, Philadelphia, was the representative of the Bureau of Medicine and Surgery in connection with the building of the U. S. S. *Relief*, the first hospital ship, which he served as its first commanding officer; was in command of the Naval Hospital, Norfolk, Va., from August 1926 to June 1930, with additional duty as medical officer in command, Pharmacist's Mates School, Naval Hospital, Norfolk; district medical officer in the Fourth Naval District, and from January until December 1931 commanded the Naval Hospital, League Island, Philadelphia; retired in December 1932; before being recalled to the service in 1943, was state medical director for Delaware and Chester counties, Pennsylvania; besides the Navy Cross, awarded him in World War I, received numerous honors for his activities in the Spanish-American War, the Boxer Rebellion and the Philippine campaign; an authority and liberal writer on venereal diseases, leprosy and bone surgery; a delegate representing the Navy Department at the fifteenth International Congress of Hygiene and Demography and Second Pan American Scientific Congress; a member of the War Relief Board, American Red Cross, 1914-1917, of the General Medical Board of Council of National Defense, 1917, of the Board for Development of Navy Yard Plans, 1916, of the Interbureau Logistics Committee, 1916-1917, of the General Munitions Board organized at the outbreak of World War I; in charge of the exhibit of the Medical Department of the Navy at the sesquicentennial exhibition, Philadelphia, which was awarded a gold medal; member of the American Association for the Advancement of Science, American Association of the History of Medicine, American Social Hygiene Association, Association of Military Surgeons of the United States and the American Public Health Association; fellow of the American College of Surgeons; senior medical officer for the V-12 program at the University of Pennsylvania; died suddenly in Darby April 2, aged 70, of edema of the lung.

**Francis Rivers Lawther,** Wilmington, N. C.; University and Bellevue Hospital Medical College, New York, 1934; member of the American Medical Association and the South Carolina Medical Association; fellow of the American College of Surgeons; interned at the Bellevue and Roosevelt hospitals in New York, where he served a residency at the Memorial Hospital for the Treatment of Cancer and Allied Diseases; served as medical director of the Berkeley County Hospital in Moncks Corner, S. C.; commissioned a captain in the medical corps, Army of the United States, on May 21, 1942; later promoted to major; chief surgeon at Kelly Field, Texas; killed in an airplane accident in Tucson, Ariz., January 20, aged 37.

**Carl Henning Mattson** ✠ St. Paul; University of Minnesota Medical School, Minneapolis, 1930; served an internship and residency at the Ancker Hospital; began active duty as a lieutenant commander in the medical corps of the U. S. Naval Reserve on Sept. 24, 1943; died in the Pacific area, January 15, aged 43, of a generalized gasoline burn received in a plane crash while on his way back to the Admiralties following his participation in the Luzon invasion.

**Frank Hugh Maxwell** ✠ Mansfield, Ohio; University of Michigan Medical School, Ann Arbor, 1930; served an internship at St. Luke's Hospital in Cleveland and a residency at the Mansfield General Hospital; began active duty as a captain in the medical corps, Army of the United States, on April 26, 1942; died in Mindora, P. I., March 7, aged 39.

**Ned Robert McKrill,** Weston, Mass.; Tufts College Medical School, Boston, 1942; diplomate of the National Board of Medical Examiners; served an internship and residency at the Charity Hospital in New Orleans; began active duty as a lieutenant (jg) in the medical corps of the U. S. Naval Reserve on Oct. 10, 1944; accidentally drowned in the Pacific area February 1, aged 30.

**Samuel Fletcher Parker** ✠ Colonel, M. C., U. S. Army, Jackson, Miss.; Hospital College of Medicine, Louisville, Ky., 1905; served during World War I; entered the medical corps of the regular U. S. Army as a major in 1920; promoted to lieutenant colonel in 1937; later promoted to colonel; stationed in Hawaii for six years; in 1925 was transferred to Western Reserve University School of Medicine in Cleveland, where for five years he was professor of military science and tactics; chief of the pediatric service at the Army General Dispensary in Washington, D. C., from 1930 to 1935 and chief of the outpatient department at Walter Reed Hospital from 1939 to 1941; chief of the medical service at Fort Monroe, Va., from 1935 to 1937, serving in the same capacity at Gorgas Hospital in Ancon, Canal Zone, from 1937 to 1939 and at La Garde General Hospital, New Orleans, from 1941 to 1943; supervised the building of Foster General Hospital, becoming its first commanding officer in 1943; died in the Kennedy General Hospital, Memphis, Tenn., February 6, aged 62, of heart failure following pneumonectomy.

**Warren David Robbins,** Cape May, N. J.; Cornell University Medical College, New York, 1926; member of the American Medical Association; past president, secretary and treasurer of the Medical Society of Cape May County; diplomate of the National Board of Medical Examiners; served as county physician and police surgeon; interned at the Philadelphia General Hospital and served a residency at St. Christopher's Hospital for Children, Philadelphia; began active duty as a captain in the medical corps, Army of the United States, Sept. 21, 1942; died in Italy Aug. 9, 1944, aged 43, of acute subarachnoid hemorrhage.

**Robert Sanderson** ✠ Arlington, Va.; Harvard Medical School, Boston, 1932; member of the Massachusetts Medical Society; diplomate of the National Board of Medical Examiners; interned at the Beverly Hospital in Beverly, Mass., and the Boston City Hospital; commissioned a lieutenant in the medical corps of the U. S. Naval Reserve on Aug. 8, 1942; stationed in the Navy Department in Washington, D. C.; died February 21, aged 41.

**Karl McCormick Scott,** Lakewood, Ohio.; University of Michigan Medical School, Ann Arbor, 1912; member of the American Urological Association; served during World War I and later in the regular U. S. Navy; commissioned a lieutenant commander in the medical corps, U. S. Naval Reserve, on July 8, 1944; died in the U. S. Naval Hospital, Portsmouth, Va., Sept. 29, 1944, aged 54, of atrophic cirrhosis of the liver.

# Correspondence

## IRREVERSIBLE ORGANIC CHANGES IN CASES OF PSYCHIATRIC DISTURBANCE

*To the Editor:*—Col. Howard A. Rusk, chief of the Convalescent Service Division, Office of the Air Surgeon, Army Air Forces, has referred to us the following problem:

"From observations in the field of 'operational fatigue,' stress reaction, anxiety state from combat and so on, there are certain endocrinologic and physiologic changes, some of which are apparently irreversible even after the psychiatric problems have been adequately treated. All pertinent data on this subject with its interpretation by experts in the field, research projects and any other material or work that could be undertaken to increase the knowledge in this field would be deeply appreciated."

I would welcome any further citations in this field.

Sincerely yours,

DAVID R. SALMON, 1775 Broadway, New York 19.
Executive Director, National
Council on Rehabilitation.

## TESTS FOR URINARY BILIRUBIN

*To the Editor:*—After reading the editorial entitled "Methylene Blue Test for Urinary Bilirubin" in THE JOURNAL, April 21, it seemed probable that a practical solution of the clinical problem of detecting small amounts of bile in the urine had been attained. According to the recent article by Myers (*J. Indust. Hyg. & Toxicol.* **27**:52 [Feb.] 1945), whose work is based on that of Franke and of Fellinger and Menkes (*Wien. klin. Wchnschr.* **46**:133 [Feb.] 1933), when 2 drops of Loeffler's methylene blue are added to 10 cc. of urine containing bilirubin the urine turns a brilliant green. Consequently the occurrence of such a "positive" test with the second normal urine specimen which we tested according to directions was disturbing. As the specimen, though containing no bile, was a concentrated, yellow sample from a normal subject, it appeared to be possible that the "positive" test was entirely nonspecific for bilirubin.

That a chemical reaction with bilirubin is clearly not involved was demonstrated by the fact that "positive" tests were observed whenever distinctly yellow but bile free specimens of urine from normal persons were tested according to Myers' directions. Moreover, when a bile containing urine was diluted with water to the same strongly yellow color as that of a concentrated normal urine containing no bile, the addition of methylene blue to each gave identical green colors. Finally, various shades of green were obtained with solutions of such different blue pigments as Loeffler's methylene blue, brilliant cresyl blue or prussian blue in such yellow or reddish yellow liquids as meat infusion broth or aqueous solutions of potassium dichromate, ferric chloride, istizin (dihydroxyanthraquinone) or hemolyzed blood.

Fellinger and Menkes, as well as Myers, expressed uncertainty but recognized that the test probably depended on a mixture of pigments. That such an optical effect was largely, if not wholly, responsible for the change of color of these dyes from blue to green when placed in the yellow liquids was made clear by the following simple experiment:

Ten cc. of distilled water was placed in a test tube, and in two similar test tubes were placed 10 cc. of one of the aforementioned distinctly yellow liquids. To one of the tubes containing the yellow liquid were added 2 drops of Loeffler's methylene blue. To the tube containing distilled water was added the same amount of dye. Now, when the test tube containing the blue dye in distilled water was viewed in daylight through the test tube containing the yellow liquid, it appeared to have exactly the same green color as did the tube of yellow liquid to which the blue dye had been added directly.

According to Myers, "the only known false positive tests encountered in these tests were found in urine containing blood and in several cases where there was an elevated temperature above 101 F." A few drops of blood hemolyzed in 10 cc. of distilled water give a yellowish red solution with slight turbidity. The urine of febrile patients is often concentrated and yellow or yellowish red. Istizin, an orange-yellow cathartic drug, when secreted in the urine also gives a false positive according to Fellinger and Menkes. However, from our experiments it appears that any sufficiently yellow liquid or urine, whether containing bilirubin or not, will give a "positive" test. Consequently it is disappointing to be forced to the conclusion that the methylene blue test merely substitutes, for the problem of whether a urine is more or less yellow, the equally subjective question as to whether after the addition of methylene blue the sample of urine appears more green than blue. Unfortunately for the usefulness of the test in the clinic, bilirubin is only one of several substances which may impart, when present in sufficient concentration, a yellow color to normal or pathologic urines.

JANET WATSON, M.D.
MANSON MEADS, M.D.
W. B. CASTLE, M.D.
Thorndike Memorial Laboratory,
Boston City Hospital,
Boston.

# Medical Examinations and Licensure

## COMING EXAMINATIONS AND MEETINGS

### BOARDS OF MEDICAL EXAMINERS
### BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Examinations of the boards of medical examiners and boards of examiners in the basic sciences were published in THE JOURNAL, May 19, page 227.

### NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: Parts I and II, July 16-18. Part III. Various centers, June. Exec. Sec., Mr. E. S. Elwood, 225 S. 15th St., Philadelphia.

### EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF INTERNAL MEDICINE: *Oral.* Philadelphia, June 6-8 and Chicago, June 27-29. San Francisco, Oct. 15-17. *Written.* Various centers, Oct. 15. Final date for filing application is Aug. 1. Candidates in the armed forces may take the examination at their station with the permission of their medical commanding officer. Asst. Sec., Dr. W. A. Werrell, 1301 University Ave., Madison 5, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: Chicago, May 28. Sec., Dr. Paul Bucy, 912 S. Wood St., Chicago 12.

AMERICAN BOARD OF OBSTETRICS & GYNECOLOGY: *Part II. Oral.* Atlantic City, June 13-19. Sec., Dr. Paul Titus, 1015 Highland Bldg., Pittsburgh 6.

AMERICAN BOARD OF OPHTHALMOLOGY: New York, June 13-16; Chicago, Oct. 4-6; and Los Angeles, January. Sec., Dr. S. Judd Beach, 56 Ivie Rd., Cape Cottage, Me.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: *Part I. Oral and Written.* New Orleans, Sept. 28-29, Philadelphia, Oct. 5-6, Chicago, Oct. 12-13 and San Francisco, Oct. 19-20. Final date for filing application is August 1. Sec., Dr. G. A. Caldwell, 3503 Prytania St., New Orleans 15.

AMERICAN BOARD OF OTOLARYNGOLOGY: Chicago, Oct. 3-6. Sec., Dr. Dean M. Lierle, University Hospital, Iowa City, Ia.

AMERICAN BOARD OF SURGERY: *Written.* Various centers, October. Final date for filing application is Aug. 1. Sec., J. S. Rodman, 225 S. 15th St., Philadelphia 2.

AMERICAN BOARD OF UROLOGY: *Written.* Chicago, Dec. 9. *Oral.* Chicago, Feb. 19-22. Sec., Dr. Gilbert J. Thomas, 1409 Willow St., Minneapolis 4.

# Bureau of Legal Medicine and Legislation

## MEDICOLEGAL ABSTRACTS

**Malpractice: Alleged Failure to Sterilize Open Wound Before Placing Fractured Leg in Cast.**—The plaintiff, a boy of 19, was struck by an automobile in Virginia, Jan. 17, 1942, and was thrown into a sandy ditch, suffering a compound comminuted fracture of the right leg, just below the knee. He was taken to a hospital in Williamsburg and given temporary attention. January 19 the defendant physician, who "specializes in bone and joint surgery," took charge of the case. According to the plaintiff there was an open wound in his lower leg with the broken bone protruding, and the defendant did nothing to sterilize or cleanse the wound except to wipe off the blood and then immediately put on a closed cast extending from the patient's toes to his groin. Thereafter gravel, sand and pus came out from the cast at the top at the groin. Eighteen days after the application of the cast the patient's brother-in-law cut an opening in the cast over the wound, and pus and sand came from the opening. Subsequently the defendant placed another cast on the leg and left a window in it for dressing. The plaintiff returned to his home in North Carolina March 6 and consulted other physicians, who on April 5 performed an operation on the leg, removing pieces of bone. Apparently on the back of the leg along which the pus had run the epidermis had been damaged or removed as a result of a malignant infection that had set in. Eventually the right leg became about an inch shorter than the other. Subsequently the patient instituted an action for malpractice against the defendant, alleging that the physician failed to use reasonable care and diligence and failed to exercise his best judgment and skill in treating him, resulting in increased pain to the patient, necessitating the operation performed in North Carolina, and causing the shortening of the leg. At the trial there was medical testimony that a failure to disinfect and cleanse the wound and limb would be improper treatment, that it would not be proper to put a cast on the leg without sterilizing the wound and that failure to sterilize an open wound with sand in it would tend to set up or increase infection. Evidence was presented on behalf of the defendant tending to show that he had properly cleaned and sterilized the wound and had treated his patient in the best approved manner. At the close of the evidence the trial court sustained a motion for a nonsuit and dismissed the action. The patient then appealed to the Supreme Court of North Carolina.

The only question presented, said the supreme court, is whether or not there was sufficient evidence adduced at the trial to require the submission of the case to the jury. On a motion for judgment of nonsuit the defendant's evidence cannot be considered unless favorable to the plaintiff, and the plaintiff is entitled to every fact and inference of fact pertaining to the issues involved which reasonably may be deduced from the evidence. The plaintiff was injured in Virginia and was treated by the defendant in that state. It follows therefore that in an action for damages for malpractice the standard of the physician's duty in the premises as affecting his liability for negligence must be determined by the law of the place in which the tort complained of was committed. The court accordingly cited a number of applicable decisions of the Supreme Court of Appeals of Virginia and from them concluded that the pertinent law in Virginia is as follows: A physician is bound to bestow on the treatment of his patient such reasonable and ordinary skill and diligence as those practicing in the same general line ordinarily exercise in like cases and one who accepts employment as a specialist must not only possess that degree of skill and knowledge ordinarily possessed by those engaged in that specialty but must also exercise his best judgment in the application of his skill and in the use of ordinary care. That degree of skill and care is to be exercised both in the performance of the operation and in the subsequent necessary treatment following. A physician, however, is not an insurer of a cure or even of beneficial results, nor is he held to the highest degree of care known to his profession. The mere fact that his treatment was not successful or was deleterious will not alone raise a presumption of negligence. The physician must exhibit only that degree of skill and diligence employed by the prudent practitioner in his field. The standard for the measurement of the skill exercised is to be shown largely by the testimony of expert witnesses, and where there is conflicting testimony of the expert witnesses as to the standard of professional skill and care, as well as to the ultimate facts on which the expert evidence is based, a question for the consideration of the jury is presented.

The principles just announced, continued the North Carolina court, are not in conflict with the standards of professional conduct established by the decisions of this court. For instance, it has been repeatedly held in North Carolina that a physician who undertakes to treat a patient implies that he possesses the degree of professional learning, skill and ability that others similarly situated normally possess; that he will exercise reasonable care and diligence in the application of his knowledge and skill to the patient's care; and exert his best judgment in the treatment and care of the case entrusted to him. *Nash* v. *Royster*, 189 N. C. 408, 127 S. E. 356; *Covington* v. *Wyatt*, 196 N. C. 367, 145 S. E. 673; *Lippard* v. *Johnson*, 215 N. C. 384, 1 S. E. (2d) 889. Accordingly this court has held that a physician may be held liable for an injury to his patient only when the injurious result flows proximately from want of that degree of knowledge and skill ordinarily possessed by others of his profession, or from the omission to exercise reasonable care and diligence in the application of his knowledge and skill to the treatment of his patient. *Davis* v. *Wilmerding*, 222 N. C. 639, 24 S. E. (2d) 337; *Groce* v. *Myers*, 224 N. C. 165, 29 S. E. (2d) 553. Specifically in the Davis case, supra, this court said:

> A departure from approved methods in general use, if injurious to the patient, suffices to carry the case to the jury on the issue of negligence.

Inferences of want of due care may be drawn from evidence tending to show that harmful foreign substances were introduced into a patient's body during surgical operations and left there. *Pendergraft* v. *Royster*, 203 N. C. 384, 166 S. E. 285; *Mitchell* v. *Saunders*, 219 N. C. 178, 13 S. E. (2d) 242. Applying these principles, it is apparent that, while there was no evidence adduced at the trial that the physician defendant did not possess requisite knowledge and skill in his profession, the plaintiff did offer some evidence of negligence on the part of the defendant with respect to his failure to cleanse and sterilize the open wound before applying the closed cast.

The physician, however, sought to justify the action of the trial court in sustaining a nonsuit on the ground that there was no substantial evidence that any negligence in this respect was the proximate cause of the result complained of. While all of the injurious results, answered the court, complained of may not be attributed to the negligence of the attending physician, if established, we think there is some evidence tending to show that suffering on the part of the patient was aggravated, another operation necessitated, and the epidermis on the patient's leg removed as a result of malignant infection set up or increased by the physician's want of due care as alleged. While the physician's evidence tended to deny the facts alleged by the patient, as well as the inferences and conclusions therefrom on which the patient's action was based, we think there was sufficient evidence produced to warrant submission of the case to the jury and that the trial court was in error in granting the motion for nonsuit.

Accordingly the judgment in favor of the physician was reversed and the case remanded for a new trial.—*Buckner v. Wheeldon, 33 S. E. (2d) 480 (N. C., 1945).*

# Current Medical Literature

## AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1935 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

### American Journal of Diseases of Children, Chicago

**69**:71-140 (Feb.) 1945

Clinical Appraisal of Infants' Head Size. J. D. Boyd.—p. 71.
*Immunity to Tetanus Induced by Third Dose of Toxoid Four Years After Basic Immunization, Based on Study of 25 Allergic Children. M. M. Peshkin.—p. 83.
Changes in Vibratory Sense of Patients with Poliomyelitis as Measured by Pallesthesiometer. W. O. Frohring, P. M. Kohn, J. F. Bosma and J. A. Toomey.—p. 89.
Normal Standards in Treatment of Young Persons with Diabetes. J. H. Barach.—p. 92.
*Erythroblastosis Fetalis in Mothers with Rh Positive Blood: Report of 6 Cases, with Comment on Isoimmunization with A and B Agglutinogens. S. H. Polayes.—p. 99.
Hemorrhagic Uremia. M. G. Peterman.—p. 103.
Congenital Ileal Atresia with Gangrene, Perforation and Peritonitis in Newborn Infant: Staged Operations: Obstructive Resection, Ileocolostomy and Excision of Exteriorized Ileum. E. E. Arnheim.—p. 108.

**Immunity to Tetanus.**—Peshkin administered to 25 allergic children, four years after completion of the basic immunization with two 0.5 cc. doses of combined alum precipitated diphtheria and tetanus toxoids, a third, or "booster," dose of 0.5 cc. of alum precipitated tetanus toxoid alone. No febrile or systemic allergic reaction occurred. Prior to the administration of the "booster" dose and from one to six months thereafter, reactions to scratch tests with undiluted combined alum precipitated diphtheria and tetanus toxoids and with alum precipitated tetanus toxoids alone gave negative results. The injection of a third or "booster" dose was followed in all instances within one month by an adequate tetanus antitoxin titer. This titer was always higher and lasted for a much longer period than that which followed basic immunization as well as that which followed administration of a "booster" dose three to fifteen months after basic immunization. The titer was comparable to the maximum antitoxin response following a "booster" dose of toxoid given two years after the basic immunization. The highest antitoxin values thus far obtained followed a "booster" dose injected three years after the basic immunization. In a child with basic immunization with two doses of combined alum precipitated diphtheria and tetanus toxoids, the third injection to be administered two to four years later should be of alum precipitated tetanus toxoid alone in order to keep local and systemic allergic reactions at the minimum level.

**Erythroblastosis Fetalis in Mothers with Rh Positive Blood.**—Polayes reports 2 cases of erythroblastosis in detail. The 2 fulfil all the clinical criteria for the diagnosis of erythroblastosis fetalis (icterus gravis neonatorum). One patient recovered after a transfusion of blood; the other died despite similar therapy. Necropsy showed the anatomic changes of erythroblastosis fetalis, including kernicterus. In both cases the mother's blood group was group O, Rh positive and the child's group A, Rh positive. The Rh factor and all its known variants, as well as the Hr antigen, were excluded as possible immunizing antigens. In both cases the anti-A agglutinin in the mother's serum showed a high titer (1:700 and 1:750), a fact which strongly suggests isoimmunization of the mother with the A antigen of the baby. Although more statistical data are required to establish the frequency of such cases, nevertheless it is believed that (*a*) isoimmunization by the A and B agglutinogens may occur and that (*b*) erythroblastosis fetalis may result from A or B isoimmunization by a mechanism similar to that already established for the Rh factor.

### American Journal of Ophthalmology, Cincinnati

**28**:243-354 (March) 1945

Ariboflavinosis. Ida Mann.—p. 243.
Space Eikonometer Test for Aniseikonia. A. Ames Jr.—p. 248.
Perforating Ocular Injuries. A. C. Snell Jr.—p. 263.
Trachoma Virus and Morphology of Inclusion Bodies. A. Loewenstein.—p. 282.
Iodide Therapy for Senile Macular Degeneration. R. G. Laird.—p. 287.
Errors in Diagnosis of Intraocular Tumors (Suspected or Real). W. E. Bruner.—p. 297.
Some Observations on Chemical Nature of Pterygium. H. H. Beard and T. J. Dimitry.—p. 303.
Bacteriologic Study of Human Conjunctival Flora. F. H. Rodin.—p. 306.

### Annals of Internal Medicine, Lancaster, Pa.

**22**:161-334 (Feb.) 1945

*Treatment of Addison's Disease by Implantation Method. C. F. Kemper.—p. 161.
Perspectives of Psychiatry. W. C. Menninger.—p. 170.
Cholelithiasis in Sickle Cell Anemia. H. S. Weens.—p. 182.
Studies on Pathophysiology of Sickle Cell Disease. R. C. Lowe and C. C. Adams.—p. 192.
Treatment of Obesity by Appetite Control: Use of Autonomic Substances and Their Synergists. L. Pelner.—p. 201.
Evaluation of Erythrocyte Sedimentation Test in Leprosy: Statistical Study of More than 2,000 Tests in More than 500 Patients. G. H. Faget.—p. 213.
Syncope on Exertion: Relationship to Coronary Artery Disease. H. T. Engelhardt and W. A. Sodeman.—p. 225.
*Calcific Aortic Valve Stenosis: Clinicopathologic Correlation of 22 Cases. N. E. Reich.—p. 234.
Aneurysms of Abdominal Aorta. J. Epstein.—p. 252.

**Implantation Therapy of Addison's Disease.**—Kemper recommends a daily dose of from 3 to 6 Gm. of sodium chloride and elimination of foods rich in potassium. If the patient is not able to carry on in his usual occupation, daily injection of desoxycorticosterone acetate should be begun until the adequate daily dosage is determined. Sodium chloride treatment should be continued. Within two or three months just enough pellets should be implanted to meet the patient's calculated need. It has been determined that one pellet of desoxycorticosterone acetate, weighing 125 mg., when implanted under the skin, gives off approximately 0.5 mg. of the hormone in twenty-four hours. If the patient's daily dosage requirement has been determined to be 5 mg. of the steroid compound, it will require implantation of ten pellets to meet his daily hormonal needs. The sodium chloride treatment should be continued. Pellets should be reimplanted about once a year. De Maio suggests implantation by means of a small trocar and glass rod obturator. The method reduces the length of the skin incision and simplifies the implantation technic. Symptoms that may develop because the implanted pellets fail to regulate the carbohydrate metabolism should be corrected by dietary supervision and supplemental adrenal extract injections. The complication of crises should be met by supplemental sodium chloride, adrenal extract and additional synthetic hormone.

**Calcific Aortic Valve Stenosis.**—Reich studied 22 necropsies in cases of pure calcific aortic valve stenosis found at Kings County Hospital from 1934 to 1942. Rheumatic fever and arteriosclerosis have been established as the etiologic factors. Subacute bacterial endocarditis with calcification is a rarer cause. The occurrence was four times greater in males than in females in the rheumatic group. Arteriosclerotic involvement occurred seven times more frequently among males. Dizziness and syncope were due to cerebral anemia. The anginal attacks were due to myocardial ischemia. Left ventricular failure manifested itself frequently in varying degrees of dyspnea. Reasons for the failure to make an accurate diagnosis were the misinterpretation of the murmur, the confusion caused by the presence of other murmurs and the lack of corroborative findings, such as a systolic thrill and absence of an aortic second sound. The presence of apical murmurs during systole was either due to transmission from the base or due to a relative mitral insufficiency caused by the dilatation of the left ventricle. Presystolic murmurs at the apex were of the Austin-Flint type. The pulse pressure was usually normal or decreased but was sometimes increased because of concomitant aortic regurgitation or hypertension. Clinical enlargement of the heart closely paralled the weight, which was increased considerably. Fluoroscopy and roentgenographic examination is capable of almost doubling the frequency of diagnosis. Left axis deviation and

T wave negativity were helpful in differentiating aortic insufficiency and mitral lesions, since these tend to produce hypertrophy in the right chambers as well, with resultant right ventricular strain. The degree of calcification closely paralleled the degree of stenosis. Cardiovascular and extracardiovascular causes of death were about equally divided. In the absence of hypertension and definite mitral valve involvement a systolic murmur at the aortic area should suggest calcific aortic valve stenosis.

## Archives of Surgery, Chicago

**50**:63-124 (Feb.) 1945

Testicular Tumors. V. Vermooten.—p. 63.
Early Repair of Neural Wounds with Penicillin Therapy. N. C. Norcross.—p. 67.
*Convulsive Factor in Commercial Penicillin. A. E. Walker and H. C. Johnson, with technical assistance of W. H. Funderburk.—p. 69.
Ménière's Disease in a Deaf-Mute. W. E. Dandy.—p. 73.
Syndrome of Trauma to Psoas Muscle. E. Michelson.—p. 77.
Experience with Calculus of Bladder in North Carolina. P. B. Price.—p. 82.
Masked Traumatic Rupture of Spleen. J. K. Narat, A. L. Vincenti and A. F. Cipolla.—p. 87.
Progress in Orthopedic Surgery for 1943: XVIII. Amputations, Apparatus and Technic. J. W. White.—p. 89.
Id.: XIX. Research. A. Steindler.—p. 97.

**Convulsive Factor in Commercial Penicillin.**—Walker and Johnson found that application of commercial penicillin to the cerebral cortex of cats, dogs, monkeys and human beings has given rise to convulsive manifestations. The antibiotic and convulsive factors of penicillin appear to be closely related, for they are affected about equally by aging, boiling and acidifying the penicillin solution and by dissolving the penicillin in alcohol. In human beings penicillin applied to the cerebral cortex in doses of 10,000 to 20,000 Oxford units may produce convulsive manifestations.

## Bulletin New York Academy of Medicine, New York

**21**:59-114 (Feb.) 1945

Combined Use of Anti-Infectives and Anticoagulants in Treatment of Subacute Bacterial Endocarditis. L. Loewe.—p. 59.
Penicillin and Sulfonamides in Treatment of Osteomyelitis and Pyogenic Arthritis. J. A. Key.—p. 87.
Histology of Normal and Diseased Pancreas. G. Gomori.—p. 99.

**21**:115-168 (March) 1945

Scientific Humanism in This Changing World: Presidential Address. W. W. Herrick.—p. 115.
Address of Retiring President. A. F. Chace.—p. 123.
Treatment of Burns and War Wounds. L. K. Ferguson.—p. 127.
Reactions of Tissues Following Infection and Their Place in Environmental Conception of Nature of Disease. W. D. Forbus.—p. 145.
Medical Libraries and Medical History. Gertrude L. Annan.—p. 163.

## Canadian Medical Association Journal, Montreal

**52**:123-226 (Feb.) 1945

Tuberculosis in Canadian Army 1939 to 1944. J. D. Adamson, W. P. Warner, R. F. Keevil and R. E. Beamish.—p. 123.
Gastrointestinal Symptoms in Cardiovascular Disease. J. W. Scott.—p. 128.
Indications for Shock Therapy in Mental Illness. L. D. Proctor.—p. 130.
Physician's Role in Protecting Worker's Health Through Control of Industrial Environment. F. M. R. Bulmer and G. R. McCall.—p. 136.
Medical Care of Industrial Worker. R. B. Robson.—p. 143.
Thiamine Requirement of Man and the Bread Problem. E. W. McHenry.—p. 147.
*Effect of Vitamin E on Impaired Kidney Function. E. Shute.—p. 151.
Toxic Reactions Following Salicylate Therapy: Review of Literature and Clinical Reports. H. Z. Sable.—p. 153.
Müllerian Duct Cyst in Male. E. Smith and A. Strasberg.—p. 160.
Sequelae Following Spinal Anesthetic. D. C. Aikenhead.—p. 162.
Role of Hemorrhage in Mortality Rates in Pregnancy and Childbirth. M. Blair.—p. 166.
Report on Use of Continuous Caudal Anesthesia in 65 Obstetric Cases. G. W. Mylks.—p. 169.
Problems in X-Ray Localization of Foreign Bodies In and About the Eye. J. A. MacMillan.—p. 173.
Gonorrheal Keratosis. W. P. Hogarth.—p. 175.
Benzene Poisoning. M. C. Dinberg.—p. 176.
Congenital Syphilis. F. Kalz.—p. 179.

**Effect of Vitamin E on Impaired Kidney Function.**—Shute presents observations on 13 women who gave evidence suggesting either chronic nephritis or impaired renal function, such as chronic edema not cardiac in nature or hypertension. In some of the women the impairment of the renal function followed toxemia of pregnancy. Whenever possible two separate tests of the kidney function were made before treatment was begun. Therapy consisted in two weeks' trial of 25 mg. synthetic alpha-tocopherol per day. At the end of the two weeks the two hour test was repeated and the patient examined for clinical improvement. Benefit was obtained in 10 of the 13 women. The histories which are presented indicate that treatment with vitamin E may improve damaged kidney function even when the damage has been of some duration. The improvement develops quickly but is transient unless therapy is continued.

## Cancer Research, Baltimore

**5**:129-192 (March) 1945. **Partial Index**

Attempts to Induce Stomach Ulcers: IV. Effects of (*a*) Cholesterol Esters Heated to 300 C. and (*b*) Cholesterol Heated to 430 C. A. H. M. Kirby.—p. 129.
Tumors Induced with Heated Cholesterol. S. Beck, A. H. M. Kirby and P. R. Peacock.—p. 135.
Response of Central Nervous System of Rat to Methylcholanthrene: Induction of Tumors Derived from Nervous Tissue. W. O. Russell.—p. 140.
Methylation and Demethylation of Certain Carcinogenic Azo Dyes in Rat. J. A. Miller, E. C. Miller and C. A. Baumann.—p. 162.
Effects of Roentgen Radiation on Thymonucleic Acid Content of Transplantable Mammary Carcinomas. R. E. Stowell.—p. 169.
Chromosomal Enlargement in Neoplastic Rabbit Tissues. J. J. Biesele.—p. 179.

## Illinois Medical Journal, Chicago

**87**:65-112 (Feb.) 1945

Present Day Status of Venereal Disease Control and Treatment. A. J. Aselmeyer.—p. 76.
Observations on Development of Silicosis. H. E. Davis.—p. 80.
Radiation Therapy in Chronic Leukemia. T. G. Clement.—p. 84.
Effects of Drugs on Electrocardiogram. T. R. VanDellen and J. R. Miller.—p. 88.
Acute Abdomen. A. Hall and A. W. Modert.—p. 91.
Cancer of Lip. D. B. Freeman.—p. 94.

## Journal of Aviation Medicine, St. Paul

**16**:1-46 (Feb.) 1945

Pressure Breathing. A. P. Gagge, S. C. Allen and J. P. Marbarger.—p. 2.
Education of Aircrew by Medical Officers. J. W. Tice.—p. 9.
National Research Council's Committee on Medical Problems of Civil Aviation. L. B. Flexner.—p. 14.
Waiver of Physical Requirements in Civilian Flying. F. C. Kinsman.—p. 18.
Physical Examinations and the Private Flier. W. R. Stovall.—p. 21.
Impressions of Field Examiner on Entering Washington Office. W. F. Smith.—p. 26.
Medical Training at A. A. F. School of Applied Tactics. M. S. White.—p. 32.

## Journal of Clin. Endocrinology, Springfield, Ill.

**5**:1-60 (Jan.) 1945

Hyalinization of Seminiferous Tubules Associated with Normal or Failing Leydig Cell Function: Discussion of Relationship to Eunuchoidism, Gynecomastia, Elevated Gonadotropins, Depressed 17-Ketosteroids and Estrogens. C. G. Heller and W. O. Nelson.—p. 1.
Id.: Microscopic Picture in Testis and Associated Changes in Breast. W. O. Nelson and C. G. Heller.—p. 13.
Hyalinization of Seminiferous Tubules and Clumping of Leydig Cells: Notes on Treatment of Clinical Syndrome with Testosterone Propionate, Methyl Testosterone and Testosterone Pellets. C. G. Heller and W. O. Nelson.—p. 27.
Vaginal Cornification Phases During Pregnancy: Their Prognostic Significance. G. J. Hall.—p. 34.
Absorption of Pellets of Progesterone. R. B. Greenblatt and L. Q. Hair.—p. 38.
*Vaginal Smear in Diagnosis of Uterine Cancer. M. Fremont-Smith, Ruth M. Graham, L. T. Janzen and J. V. Meigs.—p. 40.
Hyperplastic Disease of Adenohypophysis. J. E. Kraus.—p. 42.

**Vaginal Smear in Diagnosis of Uterine Cancer.**—Fremont-Smith and his associates report 813 cases in which Papanicolaou's vaginal smear method for diagnosis of uterine cancer was employed. Negative smears were obtained in 635. The rest were either positive or doubtful. Cancer of the uterus can be diagnosed by vaginal smear even in the early stage. The method is applicable to the screening of large numbers of women. A negative smear does not exclude cancer. A positive smear usually means cancer. In the presence of a positive smear a biopsy should be done immediately, even though there is no clinical evidence of cancer. The diagnosis of the smears is not easy. It is not an office procedure. Familiarity with the vaginal cytology is important, and training in a laboratory doing this special work is essential.

## Journal of Experimental Medicine, New York

**81**:233-314 (March) 1945

Study of Tissue Culture Cells by Electron Microscopy: Methods and Preliminary Observations. K. R. Porter, A. Claude and E. F. Fullam. —p. 233.

Passive Immunity to Poliomyelitis in Chimpanzee. H. A. Howe and D. Bodian.—p. 247.

Nonparalytic Poliomyelitis in Chimpanzee. D. Bodian and H. A. Howe. —p. 255.

Studies in Rodent Poliomyelitis: VI. Further Observations on Interference Between Murine and Simian Strains of Poliomyelitis Virus. C. W. Jungeblut.—p. 275.

Cardiotoxic Action of Preparations Containing Oxygen Labile Hemolysin of Streptococcus Pyogenes: 1. Increased Sensitivity of Isolated Frog's Heart to Repeated Application of Toxin. A. W. Bernheimer and G. L. Cantoni.—p. 295.

Cardiotoxic Action of Preparations Containing Oxygen Labile Hemolysin of Streptococcus Pyogenes: II. Inhibition of Cardiotoxic Effect by Substance Released from Frog's Heart. G. L. Cantoni and A. W. Bernheimer.—p. 307.

## Journal Industrial Hygiene & Toxicology, Baltimore

**27**:37-58 (Feb.) 1945

Toxic Properties of Silica: I. Bronchoconstrictor Effect of Colloidal Silica in Isolated Perfused Guinea Pig Lungs. G. F. Filley, J. G. Hawley and G. W. Wright.—p. 37.

Occupational Illnesses in Cotton Industries: II. Chronic Respiratory Problems. W. L. Ritter and M. A. Nussbaum.—p. 47.

Use of Methylene Blue in Testing for Bilirubin in Urine. C. P. Myers. —p. 52.

Protection of Workers Against Noise. H. Davis.—p. 56.

## Journal of Urology, Baltimore

**53**:1-264 (Jan.) 1945

Hypertension and Its Relation to Nephroptosis. W. F. Braasch and R. Goyanna.—p. 1.

Congenital Solitary Kidney: Case Reports and Consideration of Military Significance. T. F. Conroy and J. H. Walker.—p. 4.

Clinical and Statistical Study of 471 Congenital Anomalies of Kidney and Ureter. E. C. Smith and L. A. Orkin.—p. 11.

Renal Decapsulation: Review of Literature and Report of 10 Cases. B. S. Abeshouse.—p. 27.

Evaluation of Different Types of Nephrectomy: Review of 247 Cases. C. P. Mathé.—p. 85.

Conservative Surgery in Certain Benign Tumors of Ureter. S. A. Vest. —p. 97.

Rupture of Bladder: Case Report. H. J. McGee.—p. 131.

Side Effects Caused by Diethylstilbestrol and Correlated with Cancer of Prostate Gland. C. A. Wattenberg and D. K. Rose.—p. 135.

Early or Late Orchiectomy for Carcinoma of Prostate. E. P. Alyea. —p. 143.

*Analysis of 40 Cases of Carcinoma of Prostate. W. C. Stirling.—p. 154.

Carcinoma of Prostate Gland. A. Paloma.—p. 166.

Cure of Cancer of Prostate by Radical Perineal Prostatectomy (Prostatoseminal Vesiculectomy): History, Literature and Statistics of Young's Operations. H. H. Young.—p. 188.

Heterologous Transplants of Human Carcinoma of Prostate: I. Is Human Cancer of Prostate Gland Autonomous? M. H. Masina.—p. 257.

New Sound Tip for Cystoscope. W. W. Scott.—p. 263.

**Carcinoma of Prostate.**—The 40 cases presented by Stirling are divided into 4 categories: (1) those in which orchiectomy was performed, (2) those in which orchiectomy preceded or followed resection, (3) those in which resection, orchiectomy and diethylstilbestrol were combined and (4) those in which diethylstilbestrol was used. Of 4 patients subjected to orchiectomy 2 responded favorably and lived at least two years. A third patient was bedridden and had extensive metastases to the sacrum and lumbar vertebrae. He had lost 30 pounds (14 Kg.), was anemic and suffered intense pain. Within seventy-two hours after orchiectomy the pain became less, and within a week he was able to return home without taking an opiate. He died nine months later. The fourth patient died four months after orchiectomy from cachexia. The second group, in which resection preceded or followed orchiectomy, comprised 18 patients. Ten of these succumbed after an average survival of fourteen months, but none of these 10 died from prostatic causes. Early favorable responses were obtained. Of the 8 surviving patients, 5 were entirely relieved of their pain, 2 were partially relieved and 1 obtained no relief. The third group in which resection, castration and diethylstilbestrol was used comprised 12 patients, 10 of whom are living. This is the most favorable survival group in the entire series. The 2 patients who died survived for an average period of twenty-four months following operation. They were relieved of the pain but died from cachexia. In the fourth group of 6 patients for whom estrogen therapy was used alone, 3 patients are living and 3 are dead. The author concludes that castration and estrogen therapy seem to be palliative. Neither modality prevents recurrence or retards metastasis. Resection should be utilized when partial or complete obstruction of urination is encountered. Estrogen therapy is indicated for patients refusing castration or as a supplement to orchiectomy.

## Military Surgeon, Washington, D. C.

**96**:209-292 (March) 1945

Modern Concepts of International Quarantine, with Special Reference to Military Traffic. T. B. Magath and P. T. Knies.—p. 209.

Medical Problems of Submarine Warfare. C. W. Shilling.—p. 223.

Reconditioning Program in United States Army. A. Thorndike.—p. 227.

Value of Oxygen in Abdominal Surgery. W. S. Bainbridge.—p. 229.

*Equine Encephalomyelitis of Virus Type. R. Randall.—p. 233.

Organization and Operation of Veterinary Corps Food Inspection Service. H. K. Moore.—p. 237.

Suprapubic Cystostomy. F. C. Hamm.—p. 241.

Enuresis in Adult. W. Bisher.—p. 244.

Wartime Activities of Dental Corps of U. S. Public Health Service. R. S. Lloyd.—p. 246.

Present Dental Objectives and Policies of Veterans Administration. L. Y. Beers.—p. 251.

Plastic and Reconstructive Surgery. C. R. Straatsma.—p. 255.

Oral Surgery: Its Practice and Problems in Army Dental Corps. A. J. Hemberger.—p. 257.

Erythema Multiforme Exudativium or Bullosum. H. F. Robertson and T. J. Donovan.—p. 259.

Advantages of Supplemental Radiographic Studies at Time of Induction. A. C. Galluccio.—p. 262.

Observations on Morale Factors in Overseas Noncombat Service. J. M. Flumerfelt.—p. 265.

Use of Acrylics for Enucleation with Implant and as Temporary Prosthesis. M. M. Greenberg.—p. 269.

Effective Three Hour Treatment of Scabetic Patient. S. S. Rubin and H. Blank.—p. 271.

Simple Apparatus for Body Section Radiography. P. A. Robin.—p. 273.

**Equine Encephalomyelitis of Virus Type.**—Randall maintains that equine encephalomyelitis is the most important horse disease in the United States at the present time. The knowledge that the three types of equine encephalomyelitis enzootic in the Western Hemisphere (eastern, western and Venezuelan) are pathogenic for human beings and the relatively high mortality rate of the human disease emphasize their importance from the public health standpoint. The evidence is ample that the disease is transmitted through insects, particularly mosquitoes, and its control involves antimosquito measures. Horses and mules may be protected against the disease by the annual administration of chick tissue vaccines. A vaccine suitable for human use can be made available if indications for its use develop.

## Missouri State Medical Assn. Journal, St. Louis

**42**:131-192 (March) 1945

Nutritional Recovery Following Removal of All but 3 Feet of Jejunum and Half of Colon. R. Elman and J. A. Read.—p. 145.

Coordination of Medical and Blue Cross Plans. L. H. Perry.—p. 161.

## New England Journal of Medicine, Boston

**232**:241-266 (March 1) 1945

Seventy-Five Years of Public Health in Massachusetts. M. E. Champion.—p. 241.

Acute Phosphorus Poisoning: Report of Case with Recovery. T. E. Chretien.—p. 247.

Hematology. W. Dameshek.—p. 250.

**232**:267-300 (March 8) 1945

Epochs in History of Worcester District Medical Society. R. J. Ward. —p. 267.

Differentiation of Bronchiogenic Carcinoma and Pulmonary Tuberculosis. N. R. Pillsbury and J. D. Wassersug.—p. 276.

*Thermal Burns in Diabetes Mellitus. H. F. Root.—p. 279.

Hematology (concluded). W. Dameshek.—p. 280.

**Burns in Diabetes Mellitus.**—Root describes the metabolic changes which accompanied serious burns in 2 diabetic patients. A woman aged 66, who had undergone two leg amputations and who had diabetes of the typically mild degree often associated with gangrene, had not taken insulin regularly because her urine was sugar free with diet alone. The fasting blood sugar level had varied from 110 mg. to 210 mg. She entered the Deaconess Hospital with a second degree burn on the right arm and a large eschar on the left buttock. The blood sugar level was 480 mg. She received 195 units of insulin in the first two days. At first the burns showed no evidence of serious sepsis, but this later developed and she died

on the nineteenth day. A man aged 35 had had diabetes for fifteen years, which likewise was mild and controllable by diet. As the result of a severe sunburn on the shoulders and back the skin became infected, with the formation of multiple carbuncles. He developed phlebitis and osteomyelitis and later prostatic and paranephric abscesses. When hospitalized he had to be given insulin. During the period when he suffered severe sunburn and carbuncles developed, his diet was not weighed or measured and the urine was not sugar free. The failure to control the diabetes may well have been an important factor encouraging the spread of infection.

## New Orleans Medical and Surgical Journal

**97**:383-432 (March) 1945

Ruptured Intestines: Result of Nonpenetrating Trauma: Case Report. J. M. Bodenheimer.—p. 383.
*Aseptic Antenatal Thrombophlebitis (Phlebothrombosis). M. D. Steiner. —p. 385.
Certain Etiologic Factors Concerned with Headache. E. Warren.—p. 389.
Treatment of Amebiasis. J. Arosemena.—p. 392.
Effect of Vitamins on Intestinal Function. L. D. Wright Jr.—p. 400.
Filariasis. Future Problem in United States. C. D. Knight.—p. 406.

**Aseptic Antepartum Thrombophlebitis.**—Aseptic antepartum thrombophlebitis was observed by Steiner in a woman aged 36. The number of reported cases (17, including the 1 reported) is too small for significant analysis. Both unilateral and bilateral involvement occurred and both the saphenous and femoral veins with their branches were affected. Fever was seldom a part of the picture, and the diagnosis of aseptic thrombophlebitis (phlebothrombosis) was warranted. Recovery was usually complete, though not all patients went to term. The author's case differs from most of the reported cases in the early onset of the complication at the end of the third month of pregnancy, when the uterus, although enlarged, is not yet large enough to cause much pressure on the pelvic structures. The only factor in the history which can be related to the development of thrombophlebitis was the prolonged period of rest in bed to avert a threatened abortion.

## New York State Journal of Medicine, New York

**45**:337-448 (Feb. 15) 1945

Advanced Cancer of Prostate: Consideration of Value of Radical Prostatectomy in Selected Cases. A. L. Parlow.—p. 383.
Anomalies of Upper Urinary Tract. J. E. Heslin and W. A. Milner. —p. 388.
Significance of Hyperglycemia in Myocardial Infarction. E. Goldberger, J. Alesio and F. Woll.—p. 391.
Prevention of Hemorrhagic Anemia After Blood Donation in Normal Adults. S. Shapiro, C. P. Segard and Estelle N. Tabachnick.—p. 394.
Pneumatology. F. P. Ansbro.—p. 397.

## Ohio State Medical Journal, Columbus

**41**:202-296 (March) 1945

Acute Laryngotracheobronchitis. R. E. Howard.—p. 225.
Efficacy of Whooping Cough Vaccine. J. A. Garvin.—p. 225.
Rectoperineal Fistula: Unusual Obstetric Complication. W. M. Silbernagel, O. P. Burt and J. B. Patterson.—p. 231.
Blood Sedimentation Rate: Factors Influencing Its Determination and Interpretation. R. G. Lehman.—p. 233.
Use of Penicillin in Streptococcus Viridans Blood Stream Infection. K. E. Martin and R. F. Schneider.—p. 237.
Alleviation of Anxiety During Pregnancy: Series of Answers to Questions Most Commonly Asked by Patients. L. H. Biskind.—p. 239.
Anesthesia in Thoracic Surgery. N. E. Lenahan.—p. 243.
Mycotic Aneurysm of Sinus of Valsalva. C. F. Vilter and R. J. Ritterhoff.—p. 246.

## Quart. J. of Studies on Alcohol, New Haven, Conn.

**5**:527-721 (March) 1945

Relation of National Prohibition to Incidence of Mental Disease. C. Landis and Jane F. Cushman.—p. 527.
Syndrome of Alcohol Addiction. H. M. Tiebout.—p. 535.
Psychotherapy of Alcohol Addiction in Private Mental Hospital. J. H. Wall.—p. 547.
Group Psychotherapy of Alcohol Addiction. R. G. Heath.—p. 555.
Alcoholic Hallucinatory States. J. P. Norman.—p. 563.
Drinking in an Indian-White Community. J. J. Honigmann and Irma Honigmann.—p. 575.
Study of Wives of 20 Alcoholics. Gladys M. Price.—p. 620.
Science and Legal Responsibility of Drunkard. E. G. Baird.—p. 628.

## Radiology, Syracuse, N. Y.

**44**:107-212 (Feb.) 1945

Roentgen Appearance of Lobar and Segmental Collapse of the Lung: Preliminary Report. L. L. Robbins and C. H. Hale.—p. 107.
*Roentgenographic Changes in Bone Infections Treated with Penicillin. G. B. Higley and J. C. Rude.—p. 115.
Lethal Dose Studies with X-Rays. F. Ellinger.—p. 125.
Foreign Bodies in Digestive Tract. S. Brown.—p. 143.
Atypical Pneumonia with Roentgen and Pathologic Findings. H. W. Grimm and J. Denton.—p. 151.
Anatomic X-Ray Studies of Lung, Primarily for Tuberculosis. E. C. Koenig.—p. 158.
Factors Influencing Mortality in Head Injury. H. C. Voris.—p. 166.
Revascularization of Carpal Bones. J. J. Callahan, W. R. Cubbins, C. S. Scuderi and E. Hamilton.—p. 171.
Close Range Technic in Diagnostic Roentgenology. J. Arendt.—p. 177.

**Bone Infections Treated with Penicillin.**—Higley and Rude used penicillin in 25 cases of bone infection, in some of which there were old chronic infections; in these the response was not dramatic, although in the majority there was a decrease in drainage, with improvement in the general physical condition. In some of the cases it was possible to do elective surgery concurrent with the administration of penicillin, with no extension of the infection. In the acute cases which proved susceptible to penicillin, clinical improvement preceded the x-ray signs of healing and clinical recovery occurred. The authors present summaries of 6 cases which represent several types of bone infection in which definite improvement followed the use of penicillin. In general the treatment of bone infections with penicillin has been satisfactory. The response varies in individual cases. In most instances the period of active infection was considerably decreased. Roentgenographic studies in the treated cases revealed apparent arrest of the spread of the infection, with little or no sequestration of bone and little or no involucrum. There was evidence of healing, in the form of a reactive recalcification throughout the cortex of the bone, approaching the normal architecture of the bone much more closely than does the ordinary involucrum in osteomyelitis. The area of recalcification was of slightly greater density than normal bone. Since the progress of the infection was apparently arrested and the reparative process began before extensive spread, sequestration and involucrum had appeared, the resultant end sclerosis was less than has been commonly seen in extensive osteomyelitis.

## Southern Medical Journal, Birmingham, Ala.

**38**:161-228 (March) 1945

Diverticulitis: Indications for Resection. C. Rosser.—p. 161.
Isthmus Defects of Fifth Lumbar Vertebra. R. B. Raney.—p. 166.
Evaluation of Treatment in Thromboangiitis Obliterans (Buerger's Disease). E. J. C. Hildenbrand.—p. 176.
Roentgenologic Examination of Stomach with Patient Under Sodium Pentothal Anesthesia. H. E. Plenge and J. N. Ross.—p. 183.
Problems of Filariasis. L. T. Coggeshall.—p. 186.
Rheumatic Fever. W. Weston Jr.—p. 189.
*Fever Therapy with Intravenous Foreign Protein in Neurosyphilis. D. C. Smith, J. C. Shafer and A. J. Crutchfield.—p. 194.
Penicillin in Treatment of Syphilis and Gonorrhea. A. W. Neilson, F. H. Chard, L. J. Hanchett, E. Ayers, C. T. Stepita and J. Rodriquez.—p. 204.
Management of Breech Presentation. R. F. Vogt, G. W. Bryant and W. T. McConnell.—p. 206.
Factors Influencing Morbidity and Mortality Rates in Gynecologic Surgery, Based on Analysis of 500 Consecutive Cases in Private Practice. J. T. Sanders.—p. 209.
Significance of Blood Volume Alterations in Surgical Patients. E. I. Evans.—p. 214.
Relationship Between Anesthetist and Surgeon. R. F. Bonham.—p. 221.

**Fever Therapy with Foreign Protein in Neurosyphilis.**—Smith and his collaborators present the histories of 19 patients with dementia paralytica who were treated with intravenous triple typhoid vaccine. The average number of fever bouts per individual was ten. Except for those treated during 1943, no attempt was made to insulate during fever; in 1943 only blankets and hot water bottles were used. During 1944 a cradle and light technic has been developed. Ninety patients were treated with hyperpyrexia induced by intravenous triple typhoid vaccine. About 750 episodes of fever have been given, and untoward reactions have been of minor nature with the exception of a fatality in a man with moderately advanced dementia paralytica and hypertension. Of the 19 patients whose condition is described, 16 have shown clinical improvement.

## Union Médicale du Canada, Montreal

**74**:275-416 (March) 1945

Factors which Influence Function of Normal and Pathologic Thyroid. J. H. Means.—p. 278.
Action of Cortin in Burns. A. Houot.—p. 289.
Nonspecific Ulcerative Colitis: Therapeutic Observations. J. LeSage. —p. 297.
Unrecognized Syphilis: Two Clinical Observations. V. Panaccio.—p. 305.
Vertigo. J. Saucier.—p. 308.
Feeding of Children. R. Benoit.—p. 313.
Exclusion of Doubtful Paternity by Comparative Study of Blood Groups. A. Bertrand.—p. 315.

## United States Naval Med. Bulletin, Washington, D. C.

**44**:453-680 (March) 1945. **Partial Index**

*Penicillin: Progress Report Based on 1,455 Cases Treated at National Naval Medical Center, Bethesda, Md. W. M. Craig, G. J. Thompson, A. M. Hutter, E. E. Barksdale, C. C. Pfeiffer and P. V. Woolley Jr. —p. 453.
Penicillin in Pneumonia. A. G. Lueck and C. O. Edge.—p. 480.
Gram Negative Bacilli Susceptibility to Penicillin: In Vitro Experiments. M. Steiner.—p. 486.
Salt Water Ulcers of Extremities: Occurrence in Japanese Survivors. C. W. McLaughlin Jr. and J. L. Holland.—p. 494.
Transverse Incision for Repair of Inguinal Hernia. P. Shambaugh. —p. 498.
Epicondylitis of Humerus. C. E. Cooper.—p. 501.
Repair of Direct Hernia. E. V. Parsonnet.—p. 507.
External Malleolar Fracture. H. A. Barnes.—p. 509.
Rupture of Rectus Abdominis Muscle Simulating Intra-Abdominal Tumor. C. F. Ward.—p. 515.
Plight of Ulcer Patient in Military Service: Study of 306 Enlisted Personnel with Duodenal Ulcer. F. R. Hook and R. H. Keane. —p. 519.
Vitamins Essential in Nutrition. L. E. Smale.—p. 530.
Gastrointestinal Tract Disturbances: Functional Disturbances on Psychogenic Basis. W. T. Carleton.—p. 538.
Group Therapy of Psychiatric War Casualties. J. B. Dynes and F. J. Hamilton.—p. 549.
Psychologic Study of Desertion and Overleave in Navy. W. Bromberg, A. A. Apuzzo and B. Locke.—p. 558.
Functional Amenorrhea in Waves. T. B. Marwil.—p. 569.
Eosinophilia Caused by Atabrine. H. K. Russell.—p. 574.
Filariasis in West Indian Laborers. R. F. Platzer and W. K. A. Lawlor.—p. 576.

**Penicillin in Treatment of 1,455 Cases.**—Penicillin has been used at the Bethesda Medical Center in 1,455 cases. Gonococcic infections numbered 740 and syphilis amounted to 324. Of this number 250 were early cases and 237 of these remain symptom free. Of the remainder 7 have had evidence of relapse while 6 have had what appear to be new infections. The other 87 have been instances of latent infection or central nervous system involvement. The results with penicillin in gonorrhea, early syphilis and infections due to streptococci and staphylococci are better than with any drug hitherto available. Penicillin appears to be on a par with the better sulfonamides in the treatment of infections caused by pneumococci. The usefulness of penicillin in meningococcic meningitis is not yet clearly defined. The throat cultures became negative for hemolytic streptococci within two to five days in the 14 cases of scarlet fever that were treated with penicillin. Subjective improvement was noted in two or three days. Three patients with erysipelas responded promptly to penicillin. Penicillin, administered for stomatitis and Vincent's angina, gave good results. Penicillin has been used in 36 cases of acute otitis media and acute mastoiditis with satisfactory results. Penicillin is the drug of choice in abscess complicating pharyngeal and laryngeal infections, and it was effective in 2 cases of corneal ulcer. Penicillin was used in 32 cases of surgical infections, that is, in cellulitis, postoperative infected wounds, infected hematoma, infected surgical wounds and bullet wounds. Its use was successful in 27 cases. Of 29 cases of osteomyelitis 24 were successfully treated with penicillin. Penicillin has been used in 7 cases of peritonitis associated with ruptured appendix. All recovered from this complaint, although 1 patient died of a pulmonary embolus. Penicillin was found to be ineffective in tuberculosis, lymphosarcoma, carcinoma, infectious mononucleosis, chronic ulcerative colitis, leukemia, brain tumor, primary atypical pneumonia, rheumatic fever, malaria, filariasis and mumps.

## FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

## British Medical Journal, London

**1**:175-208 (Feb. 10) 1945

Medical Corps in Red Army Operations: Its Tasks and Their Fulfilment. Y. Smirnov.—p. 175.
Treatment of Gunshot Fractures of Extremities in Evacuation Hospitals of U. S. S. R. N. N. Priorov.—p. 177.
Amputation of Extremities, and Prosthesis, in U. S. S. R. N. N. Priorov.—p. 178.
Osteoplastic Reamputation of Thigh. A. Kotov.—p. 179.
Traumatic Uremia. C. G. Parsons.—p. 180.
Cephalin-Cholesterol Flocculation Reaction as Test of Hepatic Function. A. Dick.—p. 182.
Employment of Postnatal Woman. J. V. O'Sullivan and L. B. Bourne. —p. 185.

**1**:209-246 (Feb. 17) 1945

Influenza Epidemics and Influenza Viruses. C. H. Stuart-Harris. —p. 209.
Drying Penicillin by Sublimation in United States and Canada. E. W. Flosdorf.—p. 216.
Gas Gangrene After Secondary Suture of Shell Wound of Thigh. J. H. Barclay.—p. 218.
Two Cases of Tetanus. L. Cole.—p. 219.
Tibial Bone Marrow Transfusions in Infants. F. W. Gunz and R. F. A. Dean.—p. 220.

**1**:247-284 (Feb. 24) 1945

Hunterian Museum: Yesterday and Tomorrow. G. G. Turner.—p. 247.
Influenza Epidemics and Influenza Viruses. C. H. Stuart-Harris. —p. 251.
Duodenal Ileus in Newborn. V. Smallpeice.—p. 258.
Burns and Their Treatment Among E. M. S. Hospital Inpatients. Eileen M. Brooke.—p. 259.
*Treatment of Patient with Burns, with Reference to Proflavine Powder Technic. R. W. Raven.—p. 261.
Prophylaxis of Trench Foot. R. Greene.—p. 270.

**Proflavine Powder in Burns.**—Raven uses powdered proflavine for burns. Treatment is carried out under aseptic conditions. Contaminants are mopped away with isotonic solution of sodium chloride and pieces of dead tissue are lifted off. Normal skin surrounding the wound is cleansed. Blisters are evacuated by pricking with a sterile needle. Dry proflavine powder is lightly smeared over the wound, the whole lesion being thinly coated. The area is covered with one layer of wide meshed gauze impregnated with petrolatum and over this two layers of wide meshed gauze with a liberal supply of absorbent cotton. The dressing is bandaged firmly to form a pressure dressing with either plaster of paris or calico bandages. After the first redressing the time interval between dressings is increased from ten to fourteen days. Proflavine powder is dusted on the wound at each redressing. Two illustrative cases are described. A comparison of these cases shows that the general condition of the patient treated with proflavine was much better and the toxicity much less than that of the patient who had received sulfonamides both orally and locally. Proflavine powder does not retard healing, and the healed area showed a remarkable freedom from scarring, the skin being supple and of excellent quality.

## Lancet, London

**1**:167-198 (Feb. 10) 1945

Inguinal Hernia: The House That Bassini Built. W. J. M. Brandon. —p. 167.
Treatment of Thyrotoxicosis with Thiouracil. J. C. Eaton.—p. 171.
Shovelers' Fracture. J. H. Annan.—p. 174.
*Urea and Sulfonamide Treatment of Bacterium Coli Meningitis. A. D. Ecker.—p. 176.
*Allergic Reactions to Penicillin. A. N. Barker.—p. 177.
Effect of Rubber Tubing on Solutions of Penicillin. S. T. Cowan. —p. 178.

**Urea and Sulfonamide Treatment of Escherichia Coli Meningitis.**—A soldier received a penetrating wound of the brain. A meningitis due to Escherichia coli failed to respond to sulfadiazine and penicillin, but the patient recovered after receiving 2 Gm. of sulfadiazine and 30 Gm. of urea introduced into the stomach every four hours. Ecker says that combinations of sulfonamides and urea possess a bacteriostatic effect even in the presence of the sulfonamide inhibitor, para-aminobenzoic acid. Urea is a diuretic, so it is especially important to

maintain an adequate fluid intake in patients who are receiving it. The sulfadiazine level in the blood in this case ranged from 7 to 9 mg. per hundred cubic centimeters at a time when the patient was receiving 2 Gm. of sulfadiazine and 1.2 Gm. of sodium bicarbonate every four hours.

**Allergic Reactions to Penicillin.**—Barker presents 2 cases of skin reactivity to penicillin. The first patient was a medical officer, who noticed a pruritus of the face the day after he started dispensing penicillin. Two days later he went on leave and the irritation disappeared. On his return he continued to dispense the penicillin solutions, and within two days an acute dermatitis of the face and neck developed which was accompanied by edema of the upper and lower eyelids and a feeling of tightness of the rest of the skin of the face. Next day vesiculation with a serous exudate was observed on the chin. The patient stopped dispensing but continued laboratory work with penicillin. The rash subsided within a week. When all clinical signs of dermatitis had disappeared, patch tests were performed with a solution of penicillin. An eczematous reaction developed within twelve hours. The control with autoclaved penicillin was negative. The second patient was a soldier who developed a giant urticarial reaction on the trunk and the extremities after having received intramuscular injections of penicillin for four or five days. The urticaria persisted for four weeks. The patient was covered with large confluent wheals on the trunk and extremities and exhibited dermographism. Scratch and intradermal tests with penicillin produced an urticarial wheal. An autoclaved solution of penicillin did not have this effect.

## Acta Medica Scandinavica, Stockholm

**113:**467-614 (April 17) 1943

The Galactose Tolerance Test in Peptic Ulcer. E. Ask-Upmark and Elisabeth Berg.—p. 467.
*Involvement of the Central Nervous System in Mumps. H. O. Bang and J. Bang.—p. 487.
*Spondylarthritis Ankylopoietica (Spondylosis Rhizomelica) Combined with Peripheral Arthritis. H. J. N. Dekkers.—p. 506.
Hematology in Experimental Tuberculosis: The Hemogram in Anaphylactic-Allergic and Anaphylactic-Iathergic Tuberculous Guinea Pigs. K. Birkhaug and H. Schjelderup.—p. 527.
*Clinical Investigations of Methyl Alcohol Poisoning, with Special Reference to the Pathogenesis and Treatment of Amblyopia. O. Roe.—p. 558.

**Mumps Meningitis.**—During the epidemic of mumps in the winter of 1941-1942 458 patients with mumps were admitted to the Blegdams Hospital in Copenhagen. Spinal puncture was performed on 372, or 81 per cent, of these patients. Spinal pleocytosis was observed in 235 (65 per cent). Of these 235 cases 106 presented meningitis and 129 presented latent meningitis with pleocytosis as the sole indication of the disturbance of the central nervous system. There was no age predisposition, and the two sexes were equally susceptible. The severity of parotitis and the presence of other complications did not influence the incidence of meningitis. Pleocytosis varied between 3,000 and 7,000 cells per cubic millimeter of spinal fluid; high cell counts were frequent also among the cases of latent meningitis. The pleocytosis was entirely or predominantly mononuclear. The proteins were not increased, or only moderately so, the spinal sugar was normal and the spinal fluid was sterile. Manifest meningitis appeared most frequently after the onset of the swelling of the parotid glands (up to thirty-eight days after, but mostly about the fifth day), occasionally simultaneously with, and in 10 per cent of the cases before the swelling (up to seven days before). The meningeal symptoms were mild and of short duration. Encephalitis and myelitis were not observed. One case showed involvement of the labyrinth. Unilateral deafness persisted. All the remaining patients were discharged without sequels. The immediate prognosis was always good. The high incidence of meningitis suggests that meningitis is to be considered as a manifestation rather than as a complication of parotitis. This suggestion is supported by the occurrence of the so-called prodromal forms in which the meningitis precedes the parotitis and by the autonomic forms of meningitis of parotitis virus etiology but without swelling of the parotid glands. Thirteen cases presenting benign lymphocytic meningitis of the latter type were admitted to the Blegdams Hospital during the aforementioned epidemic of mumps. The parotitis virus consequently seems capable of affecting the meninges as the single organ. Epidemic parotitis is therefore to be considered as a possible etiologic factor in cases of benign lymphocytic meningitis of unknown origin. Mumps is to be considered as a general infection whose essential clinical manifestation most frequently, but not necessarily always, is a swelling of the parotid glands.

**Rhizomelic Spondylosis Associated with Peripheral Arthritis.**—Dekkers reports experience gained from 120 cases of rhizomelic spondylosis at the Consulting Office on Rheumatic Diseases in Amsterdam during the decade of 1931 to 1940. Only 10 of the 120 patients were women. Nine cases presented rhizomelic spondylosis associated with peripheral arthritis. Six of these 9 patients suffered from gonorrhea. In 4 of these patients the rheumatic complaint started in connection with this infection or was aggravated by it. Two patients suffered from rheumatic fever and 1 from a subacute polyarthritis some time before the spondylosis developed. All these cases presented the clinical picture of rheumatoid arthritis, a relatively infrequent occurrence, which made diagnosis very difficult; in fact, many years had passed before the diagnosis was clarified. Dekkers emphasizes the importance of examining the spine also in patients suffering from acute or chronic polyarthritis, especially when the patient complains of low back pain. In doubtful cases the roentgenologic examination of the sacroiliac joints and of the spine should not be omitted. Stress is laid on the necessity of not overlooking an existing spondylosis in patients suffering from rheumatoid arthritis, especially when they do not react well to gold salt injections. X-ray treatment of the spine and of the sacroiliac joints in combination with physical therapy (ultraviolet light, heat applications, exercises) may be most effective.

**Alcoholic Amblyopia.**—Roe reports 16 cases of alcoholic amblyopia in 14 men between the ages of 24 and 69 and in 2 women aged 32 and 40. The action of methyl alcohol is due to inhibition of the process of oxidation caused by formic acid. This forms, by a reversible process, a complex compound with the iron in the respiration enzyme. Acidosis follows inhibition of the process of oxidation and is due mainly to lactic acid. Amblyopia does not as a rule appear till acidosis has become severe, i. e. sometime after the manifestation of general symptoms such as nausea, headache, dyspnea and vomiting. If the eyes are exposed to strong light, amblyopia may precede clinical signs of acidosis. Increase of metabolism favors acidosis and may thereby provoke amblyopia or may aggravate it if already present. A milder course of poisoning may be manifested if ethyl alcohol is consumed just before or after the drinking of methyl alcohol, the oxidation of which is thereby checked. All signs of poisoning may be averted if ethyl alcohol is drunk repeatedly on the first day after the drinking of methyl alcohol even though it has been consumed in large quantities. It is suggested that the intake of much fluid may exert a beneficial effect on the course of the poisoning. A secondary decline of vision was observed in all the cases in which normal acuity of vision was not restored while amblyopia persisted. It is suggested that this gradual decline and the gradual developing limitation of the field of vision may be due to atrophy of the blood vessels. Strong light, fever and muscular exertion may hasten this decline. The individual predisposition is believed to play a minor part in the tolerance to methyl alcohol. Treatment of alcoholic amblyopia consists in rapid correction of the acidosis, the supply of large quantities of fluid and the protection of the eyes against light. The author recommends administration of an isotonic (1.3 per cent) solution of sodium bicarbonate, the dosage of which may be calculated according to Van Slyke's nomogram. Liberal flushing with fluid to combat dehydration and to promote profuse diuresis is suggested. Isotonic solution of sodium chloride may correct any hypochloremia present. Ethyl alcohol helps to prevent a recurrence of acidosis. Gastric lavage should not be carried out till an intravenous injection of sodium bicarbonate has been given. There was no reliable evidence in support of the assumption that lumbar puncture may be beneficial in amblyopia. Treatment with sweat baths and thyroid seems to be contraindicated.

# Book Notices

**Savill's System of Clinical Medicine Dealing with the Diagnosis, Prognosis, and Treatment of Disease for Students and Practitioners.** Edited by E. C. Warner, M.D., F.R.C.P. Twelfth edition. Cloth. Price, $9. Pp. 1,168, with 192 illustrations. Baltimore: William Wood & Company, 1944.

The present edition of this popular book has been carefully revised under the editorship of Dr. E. C. Warner, but the essential character of the book remains unchanged from Dr. Thomas Savill's original plan. For the reader who is not familiar with this type of organization, it is essentially directed at the symptoms presented by the patient, the illness from which he suffers and what can be done about it. Each chapter is divided into three parts: the symptom which may indicate disease of the organ or region under discussion and its differential diagnosis, the physical signs of disease in that region and the various methods used to elicit them, and finally the clinical classification of various maladies affecting that region and a summary of the routine procedure to be adopted. This arrangement is unique among textbooks in medicine and serves a useful purpose for medical students on clerkships and physicians in their practice. Apart from this special feature of organization the book contains much concise modern information commonly found in textbooks of medicine. Some of the newer aspects of medical progress have been added on hypertension and its mechanism, vitamin K, sulfonamide therapy, carotid sinus, effort syndrome, Rh factor, electroencephalogram and wartime entities such as immersion foot, frost bite and trench foot. Other revisions have been added in keeping with the progress of medicine since the last revision. The chapter on the central nervous system is particularly well done. However, the chief virtue of the book is its unique plan of organization and its value as a diagnostic aid. Generally the treatment given is not in keeping with our standard textbooks on medicine. It is poorly defined, lacks critical insight and is generally inadequate. For this reason its value to the reader is restricted to its diagnostic guidance, which is usually sound and in keeping with good medicine.

**L'inhibition et la facilitation dans le système nerveux central et périphérique.** Par Miguel Ozorio de Almeida, directeur du Laboratoire de physiologie de l'Institut Oswaldo Cruz, Rio de Janeiro. Les publications savantes de l'École libre des hautes études au Brésil, 1. Paper. Pp. 135. Rio de Janeiro: Atlantica Editora, 1944.

This volume is intended to be a critical presentation of what is known about inhibition and facilitation as basic functions of the central and peripheral nervous system. The bibliographic index of 258 publications presents only the most characteristic publications, omitting the better known classic treatises.

The introduction directs the attention of the reader to the process of inhibition as an essential factor in coordinated movements and in the adaptation of purposeful reactions. Inhibition and facilitation are the indispensable factors of the functions of correlation and integration. Only the most elementary facts can be understood from the antiquated aspect of being the positive results of excitation or stimulation. Twelve chapters, almost the whole volume, contain the facts pertaining to inhibition and facilitation presented in a truly enlightening, critical and evaluating manner, and fifteen pages deal with the theories of facilitation and inhibition. Chapter 1 discusses the literature on inhibition and facilitation in lower animals, chapter 2 the phenomenon of facilitation and inhibition of similar phenomena as observed in the nerves and muscles of vertebrates. The Wedensky effect regarding the conduction of faradic current in a narcotized nerve is discussed through twelve pages, but its nature remains largely obscure in spite of the work of Lorente de No and others. Chapter 3 deals with facilitation and inhibition in reflexes, demonstrated already in the classic experiments of von Goltz, clinically observed for the first time by Nothnagel and elucidated by the work of Sherrington, Bethe, Frölich and others. Facilitation and inhibition in the rebound phenomena in decerebrate rigidity and in reciprocal innervation are discussed in chapters 4, 5 and 6. Chapters 7 and 8 deal with inhibition in strychninization and in tonic reflexes. The action of higher centers on reflexes and on the activity of lower centers, constant inhibition and facilitation, reciprocal action of cortical centers and extinction are discussed in chapter 9. Chapter 10 is dedicated to the analysis of spinal shocks, as an interruption of the facilitation brought about by stimuli from higher nerve centers. In general the spinal shock results from the abolished normal equilibrium of facilitation and inhibition. In chapters 11 and 12 the author discusses the role of inhibition and facilitation in tonus and in conditioned reflexes.

Inhibition and facilitation in their phenomenologic diversity can be interpreted only as the result of variable mechanisms. So-called peripheral inhibitory nerves demonstrate basically the same properties of excitability as other nerves. The same nerves may serve inhibition as well as excitation. Inhibition does not depend on the properties of a peripheral nerve but results from the function of the central nervous system, of ganglionary centers, of neuromuscular junctions. General theories of inhibition are those of "interference," "assimilation" or "drainage." A "colloidal" theory supposes modifications of electrolyte concentration, another is based on the "refractory period." The "chemical" theory assumes the formation of inhibitory substances. It appears that the central nervous system displays functionally the same properties which characterize the peripheral nerves, but in complicated combinations.

This interesting and inspiring treatise terminates with the discussion of several modern morphologic conceptions of the process of inhibition and facilitation.

**The Male Hormone.** By Paul de Kruif. Cloth. Price, $2.50. Pp. 243. New York: Harcourt, Brace and Company, 1945.

According to the flyleaf, this book is supposed to tell the story of the discovery of the male hormone. Actually the reader will find comparatively little concerning the discovery of any hormone. If the reader is credulous, he will turn to hormones instead of vitamins to stimulate his sexual activities, relieve fatigue and make him a business tycoon.

The book is written in the inimitable style peculiar to the author. Sensitive readers may object to reference to the possibility that if Ponce de Leon in a search for the elixir of youth "had only had a few shots of testosterone" he would have "proceeded to make all the Indian maidens of the land of the blue Caribbean." Others will merely think it comical for an allegedly scientific work. It offers enthusiasm but not the caution necessary for such potent agents as hormones. Once again de Kruif relieves himself of his pent up emotions and frustrations. He states "When the medical big bugs were out to get me on the one-day syphilis cure. . . ." Is this a persecution complex?

Sex seems to be the predominant theme of the book. Early in the volume de Kruif admits worry concerning degeneration and presumably death; soon he weaves a story around the sexual properties of a hormone; then he concludes that he will continue taking methyltestosterone, a product known as the male sex hormone.

Here is a sample of de Kruifian science: "We know that both the St. Louis Cardinals and St. Louis Browns have won championships, supercharged by vitamins." Does the author know this? He insists that he will "go on supercharging myself with vitamins just to be on the safe side, since God has played the trick on us of putting not quite enough vitamins in our food, even on the best balanced diet."

The Council on Pharmacy and Chemistry of the American Medical Association, which the author admits early in the book "is an excellent body of men," is attacked for pointing out what the author himself admits in his writing, namely, that much of the material which he has used to argue his points is still in need of further investigation. The fact that the members of the Council must have sufficient facts, not theories or provocative suggestions, to recommend a drug may appear immaterial to him. While presenting the virtues of the male hormone, he fails to leave with the reader a clear impression that the male hormone like any other hormone will be effective only in certain individuals, not all, and that it alone will not prevent or cure all forms of tiredness, diseased blood vessels and other common problems. Too little attention is devoted to the many questions yet unanswered; for example, effects of overstimulating the body with blood vessels and heart just on the verge of col-

lapse; effects on other endocrine glands; effects of long continued use. Too frequently science has seen the enthusiastic promotion of substances at first claimed to be practically miraculous and harmless but which later are shown to be lacking in therapeutic efficacy and even to be harmful, especially when carelessly used.

Here is a writer who, "being only a reporter and not a doctor of medicine," becomes enthusiastic about an experiment on a horse, the outcome of which made him "feel more confident than ever" concerning experiments made on older men. After considering what he believes to be the possible virtues of "my hero, testosterone," he is disturbed apparently and writes:

> This simply scares me. This smacks of rejuvenation. This can't be so. This gives me a bad case of buck fever. It pulls my writing wallop. I can't let myself go. To be honest, I doubt my hero, testosterone, the rebuilder.
>
> This is my mood this snowy morning.
>
> I actually begin holding back and soft-pedaling other scientific facts, suggesting other astounding rebuilding virtues of testosterone. I sabotaged my hero. Well, let's out with those new facts now.

And he does.

We have then in this book an enthusiastic, if sometimes maudlin and premature, report on the possibilities, mostly sexual, of the so-called male hormone. Some of the unknown factors in the problem of the use of hormones remain to be solved; such trifles are lightly brushed over in this book. Those qualified to speak concerning endocrinology will say that the book is premature and will do more harm than good by circulation among the general population.

**Familial Susceptibility to Tuberculosis: Its Importance as a Public Health Problem.** By Ruth Rice Puffer, Dr.P.H., Tennessee Department of Public Health. Harvard University Monographs in Medicine and Public Health [No. 5]. Cloth. Price, $2. Pp. 106, with 9 illustrations. Cambridge: Harvard University Press; London: Oxford University Press, 1944.

The author has made an earnest and honest attempt to determine why certain persons fall ill with clinical tuberculosis and others do not, with the idea of applying the information to modern tuberculosis control measures. In the introduction she states that the majority of the population in many sections of the country become infected with tubercle bacilli before reaching adult life. Therefore, on the assumption that all adults are infected with tubercle bacilli, the possibility of familial susceptibility is discussed at some length. Chapters are devoted to such subjects as tuberculosis in siblings, in consorts, in parents and in children of the tuberculous, and the control of tuberculosis.

Valuable data from various studies are presented. Considerable emphasis is placed on the tubercle bacillus, but the question is frequently raised as to whether this alone is adequate to produce tuberculosis. That inherited susceptibility may be necessary to permit the development of clinical tuberculosis is discussed at some length. In the discussion of observation on those who have previously been in contact with contagious cases of tuberculosis, only persons who later have manifestations of gross lesions such as can be demonstrated by x-ray shadows or which cause illness are regarded as having developed tuberculosis. Little consideration is given to those who develop the disease to a lesser degree, the presence of whose lesions can be detected only by the tuberculin reaction or postmortem examination. All such persons actually have tuberculosis and must be considered along with those who fall ill or die.

Appropriate warning is issued of the great danger of exposure to contagious cases of tuberculosis. This applies to the known cases. In this connection the tuberculin reaction is not mentioned, which is the only accurate method of detecting the individuals who have been effectively exposed in any group. No mention is made of the vast areas in the United States where the infection attack rate has been reduced to 1 per cent or less annually, of the corresponding decline in morbidity and mortality of numerous whole counties where 10 per cent or less of the seniors in the high schools have been infected with tubercle bacilli or of the reports of the American Student Health Association, showing that only 18 per cent of college students have been infected and in many Midwestern and Western colleges and universities less than 10 per cent.

One explanation of the decline in morbidity and mortality from tuberculosis in this country is that many members of susceptible families have died, and therefore such families are greatly reduced in number. At this point one must take into consideration the vast educational program of the National Tuberculosis Association and other organizations, which has resulted in the protection of the community against infection with tubercle bacilli. Of no small significance is the almost complete eradication of tuberculosis in the bovine species. Not long ago the bovine type of tubercle bacillus was responsible for a sizable segment of both primary and reinfection types of tuberculosis among human beings in this country. If the dying out of families with familial susceptibility were capable of solving the tuberculosis problem one would expect a different situation in nations with large populations, such as China, than exists at present. There tuberculosis has been known to exist more than five thousand years, but illness and death from tuberculosis among the Chinese constituted a tremendous problem even before the present war began.

Good methods of tuberculosis control are presented, such as periodic examinations of contacts of contagious cases, including students of nursing and medicine; however, these are extremely limited. By more modern methods the disease can be practically controlled in any community without much worry about those who may have familial susceptibility.

Most of Dr. Puffer's work and analyses and references are from communities where tuberculosis is still rife, where nearly 100 per cent of the adult population is thought to be infected, a situation not greatly different from that found in many European countries at the present moment. In such places it is difficult to bring the important factors in tuberculosis control into the limelight. Under such circumstances her presentation is splendidly done. It would be fine if she could now make a similar study and publish the report of her observations from a few of the many counties in the United States where the tuberculosis mortality has been reduced to less than 10 per hundred thousand of population and where the infection attack rate among children, including those of high school age, has been reduced to one half or one third of 1 per cent.

**Aids to Orthopædic Surgery and Fractures.** By I. E. Zieve, M.A., F.R.C.S., Surgical Registrar, Charing Cross Hospital, London. Second edition. Cloth. Price, $1.75. Pp. 270. Baltimore: Williams & Wilkins Company; London: Baillière, Tindall & Cox, 1944.

In rewriting this volume, which Mr. Eric Crook of Charing Cross Hospital first wrote in 1929, Zieve discusses the effects of abnormal development, injury, inflammations and new growths on bones, joints, muscles and tendons. He discusses these same influences on the nervous system. Free reference has been made to such standard works as Watson Jones's "Fractures and Other Bone and Joint Injuries," McMurray's and Mercer's works on orthopedic surgery and Bankart's "Manipulative Surgery." The book was not intended to take the place of larger books on orthopedic surgery in general or those on special regions. Many recent American contributions to the subject are omitted. This, the smallest book on orthopedic surgery, can easily go in a side pocket. Some subjects are treated with no more than a definition. On the whole, the book is an excellent publication and is well worth the small investment.

**Experimental Studies on the Toxicity and Potential Dangers of Trinitrotoluene (TNT).** By W. F. von Oettingen, Principal Industrial Toxicologist, and others. From the Industrial Hygiene Research Laboratory, National Institute of Health. Prepared by direction of the Surgeon General. Federal Security Agency, U. S. Public Health Service, Public Health Bulletin No. 285. Paper. Price, 15 cents. Pp. 78, with 22 illustrations. Washington, D. C.: Supt. of Doc., Government Printing Office, 1944.

Trinitrotoluene has toxicity of a low order, but its manufacture and handling are not without risk to the health of the workers concerned. This series of studies raises a number of questions with respect to these hazards and brings their answers up to date by means of observations on animals and on man. The long debated question as to whether or not pure TNT is less dangerous to handle than an impure product is raised but not answered. This interim report is essential to all physicians concerned with the industrial hygiene of high explosives.

# Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

## GLUTAMIC ACID FOR EPILEPSY

*To the Editor:*—**How effective is the glutamic acid therapy of petit mal? Please give the recommended dosage and any reactions or contraindications to its use. Where can it be obtained?**

**Howard F. Munro, M.D., Freeport, N. Y.**

ANSWER.—Glutamic acid has been reported as effective in the therapy of petit mal, psychic equivalents and personality disorders in patients with epilepsy. Accurate statistics as to its value are not available; perhaps half of the patients not benefited by other means respond favorably to glutamic acid. It is not effective against major seizures and indeed may precipitate them unless the patient is receiving some other anticonvulsant. The usual procedure is to place the patient on diphenylhydantoin sodium in gradually increasing doses until symptoms of intolerance appear. Attention should be paid to hygiene and especially to getting the patient into athletic training. If minor seizures or irritability are still troublesome, glutamic acid may then be added in large doses. The average dose for an adult is 12 Gm. a day, but twice this amount may be given safely. The dose for children is roughly in proportion. As glutamic acid is a normal constituent of the diet and widely used as a flavoring, no toxic symptoms are to be expected even from massive doses. Some patients find glutamic acid slightly nauseating, however. Glutamic acid is manufactured by Parke, Davis & Company in 0.5 Gm. tablets.

Reference:

Price, J. C.; Waelsch, H., and Putnam, T. J.: *dl*-Glutamic Acid Hydrochloride in Treatment of Petit Mal and Psychomotor Seizures, THE JOURNAL, Aug. 21, 1943, p. 1153.

## THROMBOSIS OF OVARIAN AND RENAL VEINS

*To the Editor:*—**What is the clinical picture in thromboses of the left ovarian vein with and without involvement of the left renal vein? I should think that such a condition would be relatively common following operations involving the ovary and oviduct or those involving the pampiniform plexus in the male.**

**William C. Stephenson Jr., M.D., Roanoke, Va.**

ANSWER.—As far as is known, thrombosis of an ovarian vein produces no pathognomonic signs or symptoms. Occasionally a thrombosis is found in one and rarely in both ovarian veins at the time of operation for fibroids, ovarian cyst or other condition, yet questioning has failed to elicit any unusual symptoms which might be attributed to these thromboses. Likewise there seem to be no sequelae from the discovery of thromboses in an ovarian vein at the time of a laparotomy. Involvement of the left renal vein may produce signs and symptoms involving the kidney; however, thromboses of these small deeper veins rarely produce symptoms or symptom producing thromboses of the renal vein. Should such occur, however, grave symptoms of general sepsis with localizing symptoms toward the involved kidney will be definitely present.

## FREQUENCY OF URINATION IN ELDERLY MAN

*To the Editor:*—**A man aged 70 has polyuria. His father died at 73 of uremia and prostate trouble. The blood pressure of the patient is 150/90, and he weighs between 160 and 165 pounds (73-75 Kg.). He has had no sickness during life with the exception of malaria forty years ago. He is 6 feet (183 cm.) tall, of erect posture and well preserved. The polyuria is intermittent. Repeated examinations of the urine microscopically and chemically reveal no abnormalities. Recently he finds that, after sitting for awhile, on getting up he is urged to urinate; it appears that gravitation of the bulk of urine acts on the trigone and the desire to urinate is pressing. If something attracts his attention at that time the desire passes off. There is no pain in the bladder and no pain at urination. A report from a urologist indicates some hypertrophy of the prostate, especially the left lobe; the prostate is not painful on examination. There are no obstructions to urination, no dribbling, no retention or residual urine and no cystitis. The urologic consultant thinks that a neuropsychiatric condition may exist.**

**M.D., South Carolina.**

ANSWER.—In the absence of any pathologic elements in the urine, the cause of frequent micturition may be difficult to determine. It would first be desirable to ascertain the exact amount of urine that is secreted during the day and night periods and the amount of fluid intake. An apparent polyuria may be excluded in this way. The absence of any pathologic elements in the urine, and the fact that the patient's frequency is greater when he is on his feet, would suggest an irritable condition at the vesical neck or in the prostatic urethra.

Roentgenographic studies of the urinary tract are not mentioned. These should be made, particularly to exclude the possibility of prostatic stones as well as stones in the bladder; such stones may exist in the presence of a normal urine. The possibility of chronic prostatitis should also be considered. If a study of the prostatic secretion on massage reveals prostatitis, massage and instillations into the deep urethra may relieve the frequency of urination.

In view of the fact that there is some hypertrophy of the lateral lobes of the prostate gland as determined on rectal examination, it is very possible that the median lobe is similarly enlarged. Frequent desire to urinate often is brought on by an enlarged median lobe of the prostate gland protruding into the lumen of either the bladder or the urethra. In such cases the urine may be quite normal. Enlargement of the prostate gland and consequent deformity of the bladder neck may cause dysfunction of the neck of the bladder during micturition; as a result a small amount of urine may escape into the prostatic urethra and cause a frequent desire to urinate. If cystoscopy and urethroscopy show definite hyperplasia and deformity of the neck of the bladder, a transurethral resection may be considered if other means of eliminating the symptoms have failed.

## POSSIBLE FROELICH'S SYNDROME

*To the Editor:*—**A boy aged 13 had undescended testes when born. They did not descend until he had received several doses of antuitrin, and they were very small, about the size of a navy bean. At 12 he weighed 155 pounds (70 Kg.). His mentality seems to be normal, as the state of Kansas gave him a 99 plus; he makes good grades at school and has an even temper. His secondary sex development is normal. He sticks to a job very well, eats well, has a good appetite, sleeps well, does not suffer from incontinence—in fact he seems to be normal in every way except that the testes are but little larger now than a small navy bean. His height is 63 inches (160 cm.) and his weight 160 pounds (73 Kg.). What is suggested to increase the size of the testes, and what are the prospects for increasing the organs to normal size?**

**M.D., Oklahoma.**

ANSWER.—There is no hormone that will increase the size of the testis; the male sex hormone will, however, increase the size of the genitalia. It is not clear whether the boy has previously had male sex hormone or gonadotropins. Before any form of therapy is given, it would be well to get an x-ray of his skull for the possibility of detecting a pituitary disorder; he should also have a test made of the basal metabolic rate.

From the query it would appear that the boy may have Froehlich's syndrome. If this is so and the testes are atrophied he should be given male sex hormones, possibly 75 to 100 mg. per week in divided doses. This form of therapy may be continued until the desired results are obtained.

## CONGENITAL HORSESHOE KIDNEY, RENAL CALCULI AND INFECTION

*To the Editor:*—**I have a patient with a congenital horseshoe kidney. Hematuria is present and numerous small calculi are passed. The x-ray film shows several opaque shadows in the right renal silhouette. One of these calculi was analyzed; it contained calcium oxalate. Examination of the bladder urine revealed 12 to 15 pus cells, singly and in clumps, per high power field, a rare red blood cell, occasional medium sized round epithelial cells and no casts. The urine of the right kidney showed 25 to 30 pus cells, singly and in clumps, per high power field, a few epithelial cells and an occasional red blood cell. The urine of the left kidney showed a rare leukocyte, a rare small epithelial cell and rare red blood cells; no clumps of pus cells and no casts were found. Cultures of all samples of urine show Bacillus pyocaneus and a few gram positive cocci. The patient has received sulfathiazole and sulfadiazine, but there has been no improvement in his condition. His $p_H$ has been 6. Kindly give me suggestions as to treatment of this patient.**

**M.D., New York.**

ANSWER.—This patient obviously has a congenital condition which makes for a poorly draining kidney. Infection in the presence of multiple stones makes it absolutely impossible to treat this kidney successfully as far as the infection is concerned, at least until the stones have been removed. It cannot be said, however, that surgical removal is indicated, as there are many circumstances which must be known before this can be determined. The combination of infection and the presence of calcium oxalate stones is not an indication for the administration of large and intermittent doses of any one of the sulfonamide drugs or of any other type of urinary antiseptic; since they will be of benefit only for the period during which the drug is being taken. It would be better to see that this patient has large amounts of fluid to keep the urine at the $p_H$ level of 6.